CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213793Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	213793
Priority or Standard	Priority
Submit Date(s)	2020-03-27
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PDUFA Goal Date	2020-11-24
Division/Office	DDLO/OCHEN
Reviewer Name(s)	Ovidiu Galescu
Review Completion Date	2020-11-23
Established Name	Setmelanotide (RM-493)
(Proposed) Trade Name	IMCIVREE (setmelanotide) injection
Applicant	Rhythm Pharmaceuticals, Inc.
Formulation(s)	10mg/mL solution
Dosing Regimen	1mg to 3mg once daily subcutaneous injection
Applicant Proposed Indication(s)/Population(s)	Indicated for the treatment of obesity (b) (4) associated with pro-opiomelanocortin (POMC), including PCSK1, deficiency obesity or leptin receptor (LEPR) deficiency obesity
Recommendation on Regulatory Action	approval
Recommended Indication(s)/Population(s) (if applicable)	adults and children 6 years of age and older with obesity due to POMC, PCSK1 deficiency or LEPR deficiency

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Glossary

AC	advisory committee
AE	adverse event
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
LEPR	leptin receptor
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity

OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
POMC	pro-opiomelanocortin
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
RDGO	rare genetic disorders of obesity
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Setmelanotide (RM-493), proposed trade name IMCIVREE®, is a synthetic, cyclic octapeptide (8-amino acid-containing peptide) that functions as a melanocortin-4 receptor (MC4R) agonist. Setmelanotide is being developed for patients with specific genetic defects that impact the functioning of the MC4R pathway, a hypothalamic pathway critical for regulation of appetite, satiety, energy expenditure, and body weight.

The current application seeks approval for setmelanotide as treatment of obesity (b) (4) associated with pro-opiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) deficiency obesity in adults and children 6 years of age and older. These conditions are extremely rare. To date there have been approximately 50 cases of POMC deficiency and approximately 30 cases of LEPR deficiency reported worldwide. The estimated prevalence for both POMC and LEPR is <1/1000000[1]. As of 2016, only 21 cases of PCSK1 deficiency had been identified[2]. These conditions are characterized by early onset, extreme hyperphagia, and ultimately potentially life-threatening obesity. The goal of treatment with setmelanotide is to replace the missing endogenous agonist for the MC4R.

Setmelanotide is supplied as 10 mg in a 1 mL vial. The doses recommended by the applicant for this submission are:

(b) (4)

1.2. Conclusions on the Substantial Evidence of Effectiveness

[1] ORPHA:71526, ORPHA:71528; OMIM: 601665 609734 600955
[2] Endocrine Reviews, Volume 37, Issue 4, 1 August 2016, Pages 347–371, https://doi.org/10.1210/er.2015-1117

The Applicant has provided substantial evidence of effectiveness to support approval for chronic weight management in patients with POMC, PCSK1, or LEPR deficiency obesity in adults and children 6 years of age and older. The applicant submitted data from two similarly designed, 1-year, open-label clinical studies. Study RM-493-12 (Study 012), conducted in patients with POMC or PCSK1 deficiency, and RM-493-015 (Study 015) conducted in patients with LEPR deficiency. Patients were identified by clinical phenotype and confirmed by genetic testing demonstrating genetic variants in the *POMC*, *PCSK1*, or *LEPR* gene interpreted as pathogenic, likely pathogenic, or unknown significance, using American College of Genetics and Genomics (ACGM) criteria. The primary objective was met in both phase 3 studies: 8 out of 10 (80%, 95% CI: 44.4%, 97.5%) patients with POMC deficiency in Study 012, and 5 out 11 (45.5%, 95% CI: 16.8%, 76.6%) patients with LEPR deficiency in Study 015 achieved ≥10% weight loss from baseline at 1 year. The treatment differences in key secondary endpoints are all statistically significant at an alpha level of 0.05. The pivotal studies were small and uncontrolled by necessity, because of the rarity of the diseases being study. The weight loss was sustained and significant. The average weight loss in the POMC/PCSK1 study was 23.1% and in the LEPR population the average percent weight loss from baseline was 9.7%.

The Applicant sought [redacted] (b) (4)

Metabolic endpoints:

Overall there seemed to be an improvement of metabolic parameters such as lipid panel and glycemic control. There was reduction in total cholesterol, LDL-C and triglycerides as well as HbA1C and fasting glucose and increase in HDL-C in the FAS populations of both pivotal trials. These trends were prevalent in the responder subjects, however a direct relationship with Setmelanotide cannot be established outside of the substantial weight loss in these subjects.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Rhythm Pharmaceuticals has developed setmelanotide for the treatment of obesity [redacted] (b) (4) associated with POMC, PCSK1, or LEPR deficiency obesity in adults and children 6 years of age and older. My clinical review of the efficacy data supports the claim of efficacy for weight reduction. [redacted] (b) (4) My safety review concluded that Setmelanotide is well tolerated. The observed side effects of are predictable, well understood, and do not present significant safety concerns in the context of the intended-to-treat conditions.

My recommendation is approval of Setmelanotide for chronic weight management in patients with POMC, PCSK1, or LEPR deficiency. These conditions, although extremely rare, are severe, with early-onset obesity, hyperphagia and a natural history of progressive weight gain leading to early onset insulin resistance, hyperlipidemia, cardiovascular disease and other obesity associated comorbidities. At this time there is no available therapy for these conditions.

Setmelanotide therapy resulted in substantial weight reduction in POMC/PCSK1 and LEPR subjects with 80% and 46% respectively, achieving >10% weight loss at 1 year of therapy. The weight loss was sustained and significant. The average weight loss in the POMC/PCSK1 study was 23.1% and in the LEPR population the average percent weight loss from baseline was 9.7%.

Trends towards improvement were seen in other parameters such as hunger scores, waist circumference, lipids, glycemic control and quality of life, [redacted] (b) (4)

Overall Setmelanotide was well tolerated; the most common adverse events (AEs) were injection site reactions (96 %) and hyperpigmentation of the skin and hair (78%). GI complains were also prevalent with nausea (56%), diarrhea (37%), abdominal pain (33%) and vomiting (30%) being the most common. Other frequent AEs were headache and back pain. Less common but of interest were sexual events related AEs, such as spontaneous penile erection (23% of males). Setmelanotide is a centrally acting drug and psychiatric disorders were AEs of interest for the development program. Overall 46.4% of subjects had at least one psychiatric disorder related AE. The most common were depression, including depressed mood, 30%, insomnia 15% and suicidal ideation 11%. These AEs were generally severe and led to additional interventions such as anti-depressive therapy and/or hospitalization. A direct relationship between these AEs and Setmelanotide cannot be excluded.

In conclusion, I find Setmelanotide to be sufficiently safe and effective for chronic weight management in patients with POMC, PCSK1, or LEPR deficiency obesity in patients 6 years old and above. This conclusion is strictly valid for the above-mentioned indications. Appropriate labeling should reflect that the safety and efficacy of Setmelanotide has not been established for the treatment of obesity due to other conditions.

Furthermore, subjects with mutations in *POMC*, *PCSK1*, or *LEPR* may benefit from therapy if they demonstrate response on a trial basis for 12 weeks at the therapeutic dose; however, patients should discontinue treatment if lack of efficacy (as labeled) is observed.
A companion diagnostic tool is needed to ensure safe use of the product by identifying the appropriate population for which Setmelanotide is indicated. (b) (4) Testing and validation to support approval of the device application will be the subject of a post marketing commitment (PMC).
Setmelanotide is not indicated in neonates or infants due to benzyl alcohol preservative in the to be marketed formulation. The safety and effectiveness of Setmelanotide have not been established in pediatric subjects younger than 6 years old. Clinical studies of Setmelanotide did not include subjects aged 65 and over. It is not known whether they respond differently from younger subjects. There is no available data of therapy in pregnant and lactating women, as such, setmelanotide is not recommended for use during pregnancy. Due to the benzyl alcohol content lactation labeling should include the recommendation to not breastfeed during setmelanotide therapy.
Setmelanotide has not been studied in moderate or severe renal impairment and is not recommended in these patients. No dedicated study was conducted with setmelanotide in hepatic impaired patients. (b) (4) .
The multidisciplinary FDA review concluded the necessity of several post marketing requirements and commitments. A PMR to conduct a thorough QT study to evaluate the effect of setmelanotide on the QTc interval, a PMC to develop an appropriate companion diagnostic device, and a PMC to improve the performance and repeatability of the setmelanotide confirmatory ADA assay.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• POMC, PCSK1, and LEPR deficiency are caused by defects in the hypothalamic leptin-melanocortin pathway and are characterized by early onset severe hyperphagia, and progressive obesity beginning in early childhood. These patient populations are ultra-rare. It is estimated that the prevalence of obesity due to POMC deficiency is less than 0.1 per 10,000 population and due to LEPR deficiency is	POMC, PCSK1 and LEPR deficiency obesity are rare causes of monogenic obesity which result in extreme obesity, severe hunger, progressive weight gain over time and associated comorbidities (i.e. insulin resistance, hyperlipidemia).

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	approximately 0.1 in 10,000.[3] • POMC Deficiency Obesity results when neuropeptides synthesized and processed from the POMC gene are absent or deficient. Subsequent reduction in signaling through the hypothalamic MC4R pathway leads to disruption in CNS control of appetite and weight regulation. • Patients with POMC deficiency demonstrate extreme early-onset obesity and hyperphagia as core clinical features. • Some of these patients may also show additional phenotypic features specific to this genetic disorder: Reduced levels of MSH (which also stimulates the related MC1 receptor), leading to pale skin and red hair; Processing of the POMC gene with different cleavage products in the pituitary, leading to loss of ACTH and, in some patients, adrenal insufficiency. Therefore, some POMC gene defect patients may require life-long adrenal replacement therapy. •Loss-of-function mutations in the proprotein convertase subtilisin/kexin type 1 (PCSK1) gene result in defective processing of pro-peptides including POMC. In addition to early onset obesity and hyperphagia, reported features include hyperproinsulinemia, malabsorptive diarrhea, hypogonadotropic hypogonadism, and partial central defects in the adrenal and thyroid axes. • LEPR Deficiency Obesity patients may show additional phenotypic features specific to this genetic disorder besides the core clinical	

[3] Challis BG, Millington GWM. *Proopiomelanocortin Deficiency.* 2013 Dec 12. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020. Available from: https://www.ncbi.nlm.nih.gov/books/NBK174451/

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	features of early onset severe obesity and hyperphagia[4]; Frequent respiratory infections resulting from obesity and reduced immune function have been reported in children with LEPR deficiency, sometimes resulting in childhood mortality. Insulin resistance and type 2 diabetes mellitus are also often reported as complications of extreme obesity in those patients who survive childhood. • Patients with POMC, PCSK1 or LEPR deficiency obesity have progressive weight increase, which occurs at an annual rate of 7 to 10 kg per year on average.	
Current Treatment Options	• Currently, there is no approved treatment for POMC, PCSK1 or LEPR deficiency obesity. • Surgical approaches such as gastric or intestinal banding/bypass operations are ineffective because the extreme hunger of POMC and LEPR deficiency obesity patients persists post-surgery.[5] • Drug products approved for chronic weight management are not expected to result in meaningful weight loss in these rare forms of obesity.[6]	In the absence of effective medical or surgical therapies, POMC, PCSK1 or LEPR deficiency are characterized by early onset obesity, severe hunger, impaired satiety, and progressive weight gain. The early onset, severe obesity is expected to lead to metabolic disorders and CV morbidity and mortality.
Benefit	• Setmelanotide results: In the POMC/PCSK1 study, 80% of subjects (8 out of 10) achieved >10% weight loss at one year of treatment with an average percent decrease from baseline in body weight of 23.1%. In the LEPR deficiency population 46% of subjects achieved >10%	Overall, the substantial weight loss represents a clinically significant benefit with minimal safety risk to POMC, PCSK1, and LEPR deficiency obesity patients treated with

[4] Farooqi IS, Volders K, Stanhope R, et al. Hyperphagia and early-onset obesity due to a novel homozygous missense mutation in prohormone convertase 1/3. J Clin Endocrinol Metab. 2007;92(9):3369-3373.
[5] Aslan IR, Ranadive SA, Ersoy BA, Rogers SJ, Lustig RH, Vaisse C. Bariatric surgery in a patient with complete MC4R deficiency. J Obesity. 2011; 35:457-461.
[6] Srivastava and Apovian. Current pharmacotherapy for obesity. Nat Endo. 2018;14:12-24.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	weight loss at one year of treatment with an average percent decrease from baseline in body weight of 9.7%. Trends for reduction in hunger scores were observed, (b) (4)	setmelanotide. Setmelanotide therapy may lead to reduction in hunger, and improvement in cardiometabolic parameters, as well as quality of life.
Risk	• Collectively, safety data obtained to date show that adverse events commonly associated with setmelanotide include injection site reactions, skin hyperpigmentation, headache, and gastrointestinal disorders, such as nausea and vomiting. • Adverse events of interest less frequently reported included depression, suicidal ideation, and sexual adverse reaction, including spontaneous erections in males and disorders of sexual arousal in females.	Setmelanotide is generally well tolerated. Common side effects of setmelanotide, such as injection site reactions, hyperpigmentation, and gastrointestinal disorders are predictable, well understood and do not present significant safety concerns. More serious adverse reactions, including depression, suicidality, and sexual adverse events may be addressed in labeling. These conclusions are relevant or the intended to treat population and may not be generalized to other subjects.
Risk Management	• Anti-drug antibodies (ADA): The submitted anti-RM-493 ADA assay was found to not be suitable for its intended use. • Companion diagnostic tool: At this time, the required companion diagnostic tool has not been fully developed.	The ADA assay is important for future development of Setmelanotide, to ensure both persistence of effectiveness in view of positive ADAs and no cross interactions of ADAs with native signaling through MC4R. However, the native signaling through MC4R in POMC/PCSK1 and LEPR deficiency is minimal and ADA are

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		unlikely to have a clinical impact in these disorders. The diagnostic tool is necessary to ensure safe use via proper identification of the treatment population and to limit exposure to setmelanotide in patients who would not benefit from MC4R agonism.

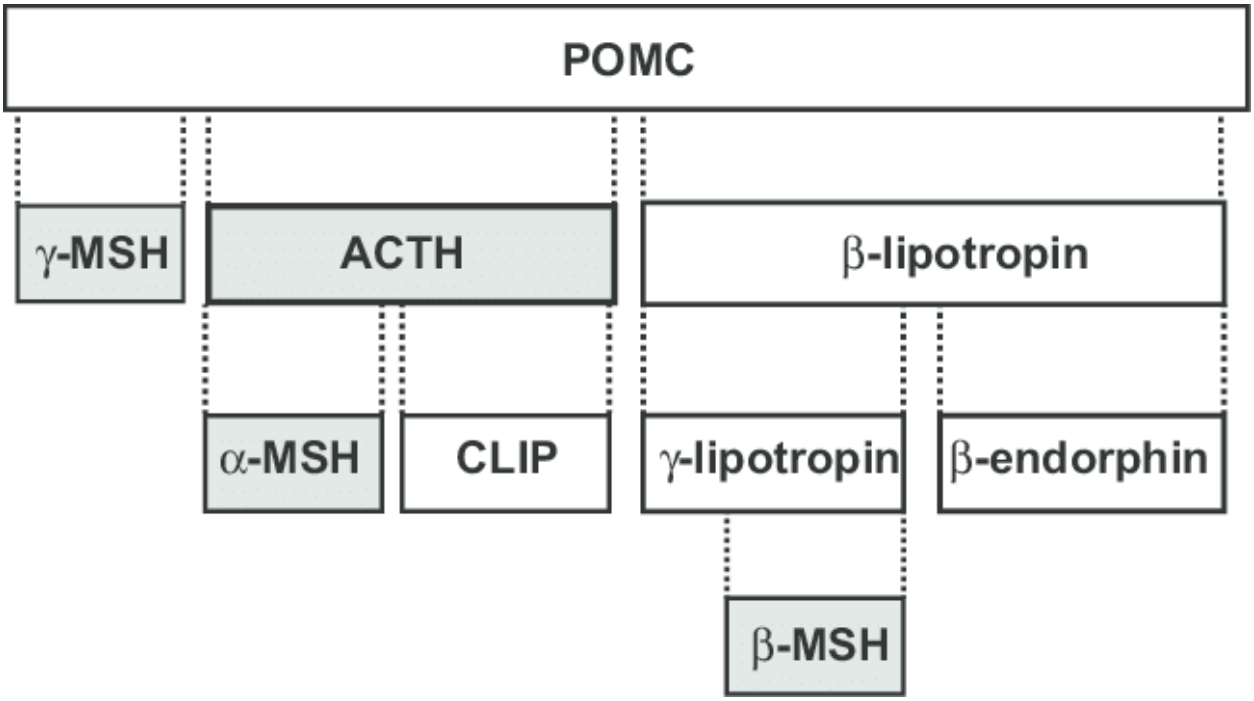
2 Therapeutic Context

2.1. Analysis of Condition

POMC Deficiency Obesity

POMC deficiency results when neuropeptides synthesized and processed from the POMC gene are absent or deficient (See Figure 1). Melanocyte-stimulating hormone (MSH) transmits the anorexic effect of leptin through the MC4R. Melanocortin 4 receptors (MC4R) may be important in regulating food intake and energy expenditure. They are predominantly located in the brain, although peripheral MC4 receptor distribution has been reported in muscle, kidney and lungs.

Figure 1 Melanocortin peptides



Melanocortin peptides (shaded boxes) derived from POMC. ACTH: adrenocorticotropic hormone; CLIP: corticotropinlike intermediate lobe peptide; MSH: melanocyte-stimulating hormone; POMC: pro-opiomelanocortin, Catania A, et al. Pharmacol Rev 2004; 56: 1-29. 1

POMC deficiency results from Loss of function mutations in the *POMC* gene. It is the most

proximal genetic defect in the MC4R pathway obesity disorders. Accordingly, affected patients demonstrate extreme early-onset obesity and hyperphagia as core clinical features. Individuals with homozygous or compound heterozygous mutations in the gene encoding the proopiomelanocortin (POMC) gene present with additional phenotypic features specific to this genetic disorder:

- Reduced levels of MSH (which also stimulates the related MC1 receptor), leading to pale skin and red hair;
- Processing of the POMC gene with different cleavage products in the pituitary, leading to loss of ACTH and, in some patients, adrenal insufficiency. Often these patients present with adrenal crisis in neonatal life due to corticotropin deficiency. Therefore, some POMC gene defect patients may require life-long adrenal replacement therapy.

PCSK1 Deficiency Obesity

PCSK1 deficiency results from loss of function mutations in the *PCSK1* gene, which encodes proprotein convertase subtilisin/kexin type 1. PCSK1 deficiency results in defective processing of pro-peptides including POMC. In addition to early onset obesity and hyperphagia, reported features include hyperproinsulinemia, malabsorptive diarrhea, hypogonadotropic hypogonadism, and partial central defects in the adrenal and thyroid axes.

LEPR Deficiency Obesity

Leptin is produced in fat cells, the placenta, and, to a lesser degree, in the gut. It signals the brain about the quantity of stored fat. This and other observations have led to the suggestion that, with increasing adiposity, resistance to the action of leptin occurs, blunting the negative feedback "adipostatic" signal to brain centers to reduce energy intake.

Leptin receptor deficiency obesity resulting from mutations in the LEPR gene are extremely rare in the general population. Patients may show additional phenotypic features specific to this genetic disorder besides the core clinical features of early onset severe obesity and hyperphagia:

- Frequent respiratory infections resulting from obesity and reduced immune function
- Alterations in immune function (decrease in the absolute CD4+ T-cell count with compensatory increase in the CD19+ B-cell count)
- Insulin resistance and type 2 diabetes
- Normal linear growth but reduced adult height
- Delayed puberty due to hypogonadotropic hypogonadism

2.2. Analysis of Current Treatment Options

Currently, there is no approved treatment for the obesity and insatiable hunger associated with POMC or LEPR deficiency obesity. The long term and cumulative impact of the significant excess body weight suggests high morbidity and mortality often beginning at a young age. Although some of the related non-obesity endocrine manifestations can be managed by hormone replacement therapy (ACTH, L-thyroxine, sex hormone replacement, etc.) no options exist to treat hunger, impaired satiety, decreased energy expenditure, or resulting weight gain. Drugs approved for general obesity are not effective in producing meaningful weight reduction in these rare cases of monogenic obesity. This lack of efficacy is not surprising because these general obesity medicines do not address the underlying MC4R pathway signaling defects that lead to obesity.

Furthermore, surgical approaches such as gastric or intestinal banding/bypass operations are generally ineffective because the extreme hunger of POMC and LEPR deficiency obesity patients persists post-surgery. This results in continued excessive food consumption, often leading to anatomical complications.

The absence of drug therapy and unsuitability of surgical intervention leaves only lifestyle modification (i.e. diet and exercise) as available therapeutic interventions for patients with severe obesity. These, however, are rarely successful over the short-term and almost never effective in the long-term due to the intense drive to eat caused by the absence of satiety signals.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Setmelanotide is a new molecular entity (NME) and is currently not marketed in the U.S. The Applicant does not seek additional indications in another division of OND at this time.

3.2. Summary of Presubmission/Submission Regulatory Activity

On 12 October 2011, Rhythm Pharmaceuticals opened IND 112595 to pursue development of RM-493 for treatment of obesity.

The following key meetings and correspondence related to this application occurred between the FDA and Rhythm, the IND sponsor:

- A Type C meeting on 1 May 2013, to discuss general principles for developing limited severe obesity indications (such as heterozygous loss-of-function of MC4R), and development pathways to achieve that goal. The necessity of development of a companion diagnostic test.
- A Type C meeting on 26 August 2015 to discuss development of setmelanotide for

(b) (4) to treat deficiencies in the leptin-POMC-MC4R hypothalamic pathway. The necessity of a thorough QT study was agreed upon given that other melanocortin 4 receptor agonists have been shown to have significant elevations in blood pressure and heart rate. At this time the agency stressed the importance of validating any hyperphagia questionnaires intended for use as well as the need for specificity for the studied condition for any PRO intended to be used. Furthermore, FDA emphasized that effects on subjective endpoints would need to be very well supported, especially given the concerns regarding the ability to blind the treatment allocation due to skin pigmentation caused by Setmelanotide. The company was encouraged to develop a suitable instrument prior to phase 3 studies. The clinical outcomes assessment (COA) staff stated that they were open to working with the sponsor to develop an instrument.
Given the rare disorders targeted, a randomized discontinuation with and/or cross-over study design was agreed upon.

- A type B meeting on 13 April 2016 to discuss development of setmelanotide for treatment of POMC deficiency obesity. The company reiterated that they understood that the hunger score instrument was not validated (b) (4) FDA reiterated that the sponsor should submit their instrument for review and comment. COA staff reaffirmed openness to further discussion with the sponsor on their instrument to increase the likelihood of success of their measurement strategy. Titration schedules were discussed for adults and pediatric subjects. The agency reiterated its interest in the overall effect of the drug regardless of adherence to treatment, and as such, emphasized that all observed data, including post-treatment discontinuation data, should be included in the primary analysis.
- A type C meeting on 25 January 2017 to discuss the continued clinical development of setmelanotide for treatment of POMC deficiency obesity.
The addition of LEPR-deficient subjects to the development program was discussed and agreed upon. (b) (4)
- A type C WRO meeting on 28 February 2017 to discuss the requirements for identifying patients with POMC deficiency obesity.
- Deferral of carcinogenicity studies (transgenic mouse (b) (4) to the post-marketing period (21 December 2017)
- A Type C meeting on 20 December 2017 to discuss the proposed statistical analysis plan (SAP) for the phase 3 protocol RM-493-012. The sponsor proposed two analysis populations to evaluate the primary and key secondary endpoints. The Full Analysis Set (FAS) consisted of all subjects who received at least 1 dose of study medication and had a baseline and at least 1 post-baseline efficacy assessment performed for the primary endpoint. The Designated Use Set (DUS) consisted of subjects who received at least one dose of study drug, experienced ≥5 kg weight loss (or 5% of body weight if <100 kg at

baseline) at the end of the initial 10-week open-label period, and proceeded into the double-blind, placebo withdrawal period. (b) (4) . The Division disagreed with this (b) (4) In an attempt to minimize the risk of type 1 error despite small samples the Division proposed the use of a categorical endpoint to test whether the proportion of all treated patients who experience at least a 10% reduction in weight is greater than 5%.
The sponsor and FDA agreed that a categorical endpoint should be used for the primary analysis.

- A Type B pre-NDA meeting on 27 August 2018 to discuss submission of a New Drug Application (NDA) for setmelanotide and resolve potential issues prior to the preNDA meeting. The division and the sponsor agreed that substantial evidence would be required to support a treatment indication (weight loss) and (b) (4) the possibility of presenting data regarding effects on hunger (b) (4) in labeling (e.g., Section 14).
A rolling review submission was agreed upon as per the Expedited Programs Guidance. Both parties established that the efficacy would be derived from the data from the to-be-marketed formulation, and the safety database would include information from all clinical studies, including studies conducted with earlier formulations.
Regarding the companion diagnostic (CDx), the Division explained its position that the absence of complete development of a CDx at filing would not preclude submission or review of the NDA, so it should not affect the timing of NDA submission. The Division stated that completing development of the CDx as a postmarketing commitment or post-marketing requirement was a possibility, assuming that upon review, there were no issues related to efficacy or safety that would necessitate a CDx at the time of approval.
GTTG clarified differences between setmelanotide and therapies for other genetic diseases that do not require a CDx. In this situation, although the drug would be indicated for patients with defects in specific genes (*POMC*, *LEPR*), genetic testing for POMC and LepR deficiency does not appear to be the current standard of care for treating obese patients (including early-onset, severe obesity).
CDRH clarified that based on the risks associated with setmelanotide therapy, it seems that a de novo premarket submission rather than a premarket approval (PMA) would be appropriate for a companion diagnostic for setmelanotide therapy. CDRH added that if an in vitro diagnostic test is needed for safe and effective use of setmelanotide therapy,

an FDA cleared, or approved test would be needed.

- A type B meeting on 27 November 2018 to discuss plans for development (b) (4) formulation of setmelanotide.
- An additional Type B pre-NDA meeting on 27 September 2019 to obtain guidance and reach agreement on the organization and presentation of data in the application.
  FDA provided clarification that, both cross-reactivity of alpha-MSH in the RM-493 ADA assay and potential cross-reactivity of antibodies to alpha-MSH with RM-493 drug would be expected to be addressed in the NDA. FDA also stated that they concurred with the sponsor proposal (b) (4) as a post-approval submission, due to delays in assay development. The agency and the sponsor agreed that a detailed analysis plan specifying the sponsor's proposed approach to evaluating the hunger endpoint(s) using two separate questionnaires (a PRO for older patients ages 12 and above; a ClinRO for younger patients ages 6-11), would need to be submitted for review.
  A preliminary discussion was held on the need for a REMS, other risk management actions and, where applicable, the development of a Formal Communication.
- The final amended request for Rare Pediatric Disease Priority Review Voucher, to treat children with POMC deficiency obesity and LEPR deficiency obesity, was submitted on 29 Jan 2020 to the Office of Orphan Products.
  – Original request was submitted in December 2016, subsequently extended for amendment to 04 Feb 2020

Setmelanotide has been granted:

- Orphan Drug Designation on 04 Apr 2016 for treatment of POMC deficiency obesity due to mutations in the POMC gene
- Orphan Drug Designation on 27 Nov 2017 for the treatment of LEPR deficiency obesity
- Breakthrough Therapy Designation (BTD) on 01 May 2017 for disorders involving genetic defects upstream of the MC4 receptor in the leptin-melanocortin pathway
  – Note: On 18 Dec 2016, Rhythm received BTD status specifically for POMC deficiency obesity. This original BTD was withdrawn on 09 May 2017 because POMC deficiency obesity is a subset included within this broader indication

3.3. Foreign Regulatory Actions and Marketing History

N/A

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The Office of Scientific Investigations (OSI) conducted investigations of two clinical sites in addition to the sponsor and concluded that the inspectional findings support validity of the data reported by the sponsor.

The initial inspection assignment planned to conduct inspections of five clinical investigator sites and the sponsor, covering Studies RM493-012, RM493-015, (b) (4). Studies 012 and 015 are pertinent to the indication. (b) (4)

The inspection of Dr. James Swain/Scottsdale, AZ (Site 006, Study RM493-102) demonstrated adequate adherence to the regulations and the investigational plan, and no objectionable conditions. (b) (4) Inspection of the sponsor, Rhythm Pharmaceutical, Inc. Boston, MA revealed adequate adherence to the regulations and the investigational plan and no objectionable conditions.

The ongoing COVID-19 global pandemic limited the ability of the Office of Regulatory Affairs (ORA) to conduct onsite foreign GCP inspections. As a result, inspections of Dr. Allison Bahm/Canada (Site 004, Study RM493-012), Dr. Karine Clement/France (Site 002, Study RM493-015) and Dr. Peter Kuehnen/Germany (Site 001, Study RM493-012) were not conducted. Remote data investigation of source records by ORA was not feasible due to local restrictions.

4.2. Product Quality

The recommendation from the Office of Pharmaceutical Quality (OPQ) is approval, which includes an acceptable recommendation for the facilities listed in the application.

Background:

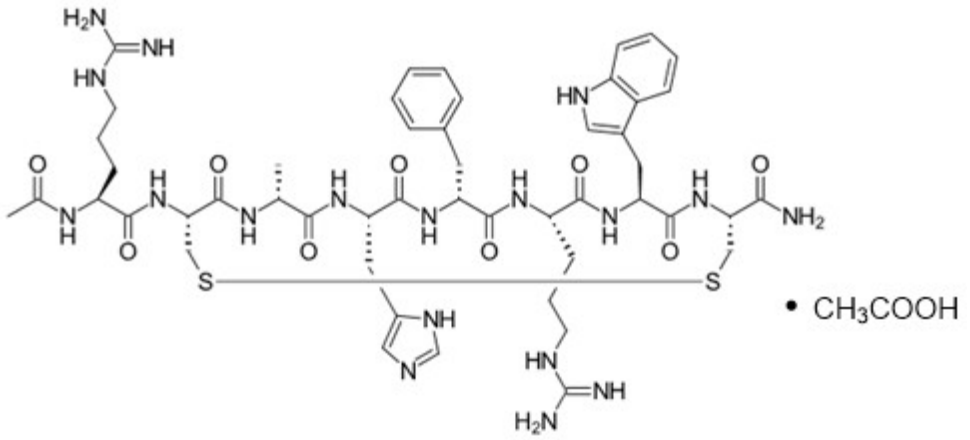
The drug substance is a synthetic cyclic octapeptide. Setmelanotide injection is a sterile, (b) (4) solution packaged in multi-dose vial/ (b) (4) stopper with 24 months of long-term stability (2-8°C) and 30 day in-use stability data. The dose will be administered using a

[redacted] syringe. Each mL of IMCIVREE contains 10 mg of setmelanotide, 100 mg of mPEG-200-DSPE [redacted] 8.0 mg of carboxymethyl cellulose [redacted] 11.0 mg of mannitol [redacted] 5.0 mg of phenol [redacted] 10.0 mg of benzyl alcohol (preservative), and 1.0 mg of sodium edetate [redacted] water for injection.

Chemical name:
Acetyl-L-arginyl-L-cysteinyl-D-alanyl-L-histidinyl-D-phenylalanyl-L-arginyl-L-tryptophanyl-L-cysteinamide cyclic (2→8)-disulfide

Structural Formula:
The structure of the drug substance, a cyclic octapeptide with a disulfide ring Figure 2.
The drug substance is prepared as the acetate salt.

Figure 2 chemical structure



Molecular formula:
C49H68N18O9S2 (anhydrous, free base)

Dr. Joseph Leginus reviewed the chemistry, manufacturing, and control information for the drug substance including manufacturing process description, the proposed starting material specifications, control strategy for impurities, characterization data for drug substance and its impurities, reference standard information, test method descriptions and methods validation, drug substance specifications, and stability data. His review concluded that the drug substance information is adequate to control the identity, purity, strength, and quality of the drug substance used for manufacturing the drug product. The proposed drug substance specifications are consistent with batches used in clinical, nonclinical, and registration stability studies.

Dr. Ted Carver reviewed the drug product information including drug product composition, drug product specification, excipient information, analytical methods, container closure system, compatibility information, and stability data. The compatibility of the active ingredient with

excipients and the container closure components is supported by drug product stability data.

For detailed information on the manufacturing process and process control, refer to Dr. Janoria's process review in Panorama dated 8/20/2020. The process review concluded that the proposed drug product manufacturing process controls are adequate to support the NDA.

For additional information, please refer to the following:

- CMC reviews in Panorama: Dr. Leginus drug substance review dated 7/16/2020,
- Dr. Zheng's microbiology review dated 2/04/2020,
- Dr. Carver's drug product review dated 8/21/2020
- Dr. Janoria' s process reviews dated 8/19/2020.
- Dr. Ted Carver granted categorical exclusion from submitting environmental assessment. Please refer to drug product review dated 8/20/20 for additional information.

4.3. Clinical Microbiology

The Microbiology reviewer, Dr. Zheng reviewed the microbiological controls used in the drug product manufacturing process including (b) (4), drug product specifications for sterility, container closure integrity, endotoxin, (b) (4) depyrogenation and (b) (4) media fill studies, (b) (4) and post-approval stability commitment. Dr. Zheng also reviewed the (b) (4) information provided in Type V DMF (b) (4). Her review concluded that the proposed microbiological controls are adequate to support the NDA. Refer to CMC (Microbiology) review by Dr. Zheng dated 2/04/19 in Panorama.

4.4. Nonclinical Pharmacology/Toxicology

The Pharmacology/Toxicology reviewer recommends approval of setmelanotide, with a post-marketing requirement (PMR) for a carcinogenicity study.

Per Dr. Theodore's review, the nonclinical pharmacological findings predict response in genetic forms of obesity with reduced melanocortin production. In vitro, setmelanotide binds to human MC4R and activates the receptor. In mice lacking MC4R function due to gene deletion, setmelanotide produced no pharmacological effects, whereas in rat and monkey models of obesity with intact MC4R function, setmelanotide produced dose-dependent decreases in food intake and body weight. Decreases in body weight in obese mice were associated with decreases in adiposity, and improved glucose tolerance and insulin sensitivity. There were no notable CNS effects in rats at exposures up to 250 times higher than clinically relevant exposures, and no effects on heart rate or blood pressure in safety pharmacology and chronic toxicity studies in monkeys.

Setmelanotide activated human MC1R and MC3R in vitro with 20-fold lower potency compared to MC4R but had no detectable activity at human MC2R and MC5R. Setmelanotide caused reversible, dose-dependent increase in skin pigmentation in monkeys, without evidence of melanocyte hypertrophy or hyperplasia following chronic dosing.

Aside from injection-site reactions, no important systemic toxicity in chronic toxicity studies, juvenile toxicity studies, or reproductive and developmental toxicity studies were identified.

Severe injection-site reactions associated with a novel excipient, mPEG-DSPE, limited the maximum doses of setmelanotide using the clinical formulation to 3 mg/kg/day in rats and 1 mg/kg/day in monkeys (9- and 26-times clinical exposures at the MRHD of 3 mg) in chronic toxicity studies. Setmelanotide formulated in saline was used to allow administration of higher doses of 15 mg/kg/day in rats and 3 mg/kg/day in monkeys (49-times and 38-times MRHD, respectively). The saline formulation also caused injection site reactions but of less severity.

Juvenile toxicity studies in rats identified no new target organs compared to adults, and no adverse effects on growth, organ development, or behavior at doses up to 15 mg/kg/day setmelanotide in saline and at 3 mg/kg/day with mPEG-DSPE (33- and 7-times the MRHD).

Reproductive toxicity studies in rats and rabbits demonstrated no adverse effects up to the highest dose of 5 mg/kg/day (11-times the MRHD), despite expected, dose-related reductions in maternal food consumption and body weight gain. There were no effects on male fertility in the chronic rat toxicity study. In an embryo-fetal development study of setmelanotide in rabbits, there was no evidence of any adverse effects independent of effects associated with reduced maternal body weight gain.

In a pre- and post-natal development toxicity study in rats, a dose-dependent decrease in body weight gain and food consumption was observed during the gestation period in maternal animals at clinical exposures, but reproductive performance and pup viability were not affected, and there were no notable adverse findings in the F1 generation at up to the highest dose of 5 mg/kg/day (7-times the MRHD).

Setmelanotide was not genotoxic in standard assays. The Pharm/Tox review concluded that the weight of evidence indicates minimal carcinogenic concern for setmelanotide in the intended population. A carcinogenicity assessment in a 6-month Tg rasH2 mouse study, and possibly a lifetime rat study (depending on the outcome of the Tg mouse study), will be conducted under a post-marketing requirement (PMR) to assess carcinogenicity.

4.5. Clinical Pharmacology

The Clinical Pharmacology review by Dr. Sista, Dr. Kitabi, and Dr. Drozda, found the clinical pharmacology data submitted acceptable to support approval of the NDA.

Per the clin/pharm review the primary evidence of effectiveness for the proposed dosing regimen from the two pivotal efficacy studies conducted in patients with POMC/PCSK1- and

LEPR-deficiency obesity, demonstrated that setmelanotide was effective on the primary endpoint in adults and children 6 years of age and older.

The recommendations are that setmelanotide should be injected subcutaneously once daily, at the beginning of the day, without regard to the timing of meals, in the abdomen, thigh, or arm, rotating to a different site each day. The drug product should not be administered intravenously or intramuscularly. If a dose is missed, the once daily regimen should be resumed as prescribed with the next scheduled dose.

For adult patients and pediatric patients 12 years of age and older, the recommended starting dose is a 2 mg once daily subcutaneous injection. After 2 weeks, the dose can be increased to a 3 mg once daily subcutaneous injection. If dose escalation is not tolerated, patients may maintain administration of the 2 mg once daily dose.

For pediatric patients ages 6 to 11, the starting dose of IMCIVREE is a 1 mg once daily subcutaneous injection. After 2 weeks, the dose can be increased to 2 mg once daily. If the dose is tolerated and additional weight loss is desired, the dose may be increased to 3 mg once daily. The proposed doses in pediatric populations are supported by population PK and exposure-response analysis.

Dose adjustment of setmelanotide is not required for mild renal impairment. Setmelanotide is not recommended in patients with moderate and severe renal impairment. Setmelanotide was not evaluated in hepatic impairment.

4.5.1. Mechanism of Action

The mechanism of action is activation of the leptin-melanocortin pathway through MC4R agonism. The MC4 pathway serves a critical role in the control of food intake and energy balance. Activation of MC4R, the final step in the signaling pathway, decreases appetite and caloric intake, and increases energy expenditure. Under normal conditions, POMC neurons are activated by brain satiety signals, including resulting from the hormone leptin acting through LEPR. POMC neurons produce a protein which is specifically processed by the PCSK1 enzyme into melanocyte stimulating hormone, or MSH, the natural ligand, or activator, for MC4R. When genetic mutations disrupt this pathway, the result is dysregulation of appetite, satiety, and energy expenditure, resulting in severe obesity. Setmelanotide targets MC4R, with the putative effect of restoring regulation of food intake and energy balance via the pathway.
Short-term administration of setmelanotide increases resting energy expenditure (REE) and shifts substrate oxidation to fat in obese individuals. Setmelanotide increased resting energy expenditure (REE) vs. placebo by 111 kcal/24h (6.4%) on average. Total daily energy expenditure (EE) trended higher while the thermic effect of a test meal and exercise EE did not differ significantly. No adverse effect on heart rate or blood pressure was observed.

4.5.2. Pharmacodynamics

The mean apparent volume of distribution after SC administration is about 49 L, and the plasma protein binding of setmelanotide is 79.1%. Setmelanotide does not appear to be metabolized by human hepatic microsomes and hepatocytes. Trace amounts of two urine metabolites, M19 and M7, were observed in a small number of subjects. The total apparent steady-state clearance of setmelanotide is about 4.86 L/h. At steady state, approximately 39% of the administered setmelanotide dose is renally eliminated as unchanged drug within 24 hours post-dose.

4.5.3. Pharmacokinetics

Following SC injection of setmelanotide, plasma concentrations of setmelanotide reached maximum concentrations at a median Tmax of 8.0 h after dosing. Steady-state plasma concentrations of setmelanotide is achieved within 2 days with daily dosing of 1-3 mg setmelanotide. The accumulation of setmelanotide in systemic circulation during once-daily dosing over 12 weeks was approximately 30%. Setmelanotide generally exhibits dose proportional PK following multiple-dose SC administration in the proposed dose range (1-3 mg).

4.6. Devices and Companion Diagnostic Issues

DTPM consistently advised Rhythm during development that it appeared that a companion diagnostic would be necessary to ensure safe and effective use of the drug, consistent with the 2014 FDA Guidance for Industry regarding In Vitro Companion Diagnostic Devices. Although generally the device should be approved concurrently with the New Drug Application, Rhythm had not yet submitted the device application at the time of the Mid-Cycle Communication held on July 22, 2019. At the meeting, the Division clarified that although there are exceptions to concurrent approval that were discussed at previous meetings between the Agency and Rhythm, these would apply only if the Agency determines during NDA review that the in vitro diagnostic is not necessary to safe and effective use of the product, and that although the review was ongoing, it appeared that the exceptions may not apply, since the pivotal studies used genetic testing to identify the study population, and genetic testing would be necessary to identify the intended target population for the marketed product.

(b) (4)

4.7. Consumer Study Reviews

N/A

5 Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

A tabular listing of all the submitted studies is available in the Appendix. For the proposed indication studies RM-493-012 and RM-493-015 were used. See Table 1 for a brief description of the relevant studies.

Table 1. Relevant studies for the proposed indication.

Study ID and population	Objective(s) of the Study	Study Design	Dosing	N	Duration of Treatment
RM-493-012 POMC deficiency obesity due to biallelic, loss-of-function POMC or proprotein convertase subtilisin/ kexin type 1 (PCSK1) gene mutations	Primary • To demonstrate statistically significant and clinically meaningful effects of setmelanotide on percent body weight change in patients with pro-opiomelanocortin (POMC) deficiency obesity due to rare bi-allelic or loss-of function mutations at the end of 1 year of treatment. Secondary To assess the effect of setmelanotide, over one year, on: • Safety and tolerability of setmelanotide (including blood pressure [BP] and heart rate [HR]). • Hunger for patients ≥12 years of age. • Percent change in body fat mass.	Open label with 8-week double blind placebo-controlled withdrawal period;	Up to 12-week dose titration to therapeutic dose level (maximum of 3.0 mg) followed by 10 weeks at therapeutic dose followed by 8-week double blind placebo withdrawal and 32 weeks continued treatment at therapeutic dose; SC injection	14	52 weeks
RM-493-015 Bi-allelic, homozygous or compound heterozygous (a different gene mutation on each allele) genetic status for either the LEPR genes, with the loss-of-function (LOF) variant for each allele	Primary • To demonstrate statistically significant and clinically meaningful effects of setmelanotide on percent body weight change in patients with LEPR deficiency obesity due to rare bi-allelic or loss-of function mutations at the end of 1 year of treatment. Secondary To assess the effect of setmelanotide, over one year, on: • Safety and tolerability of setmelanotide (including blood pressure [BP] and heart rate [HR]). • Hunger in patients ≥12 years old.	Open label with 8-week double blind placebo-controlled withdrawal period;	Up to 12-week dose titration to therapeutic dose level (maximum of 3.0 mg) followed by 10 weeks at therapeutic dose followed by 8-week double blind placebo withdrawal and 32 weeks continued treatment at therapeutic dose; SC injection	13	52 weeks

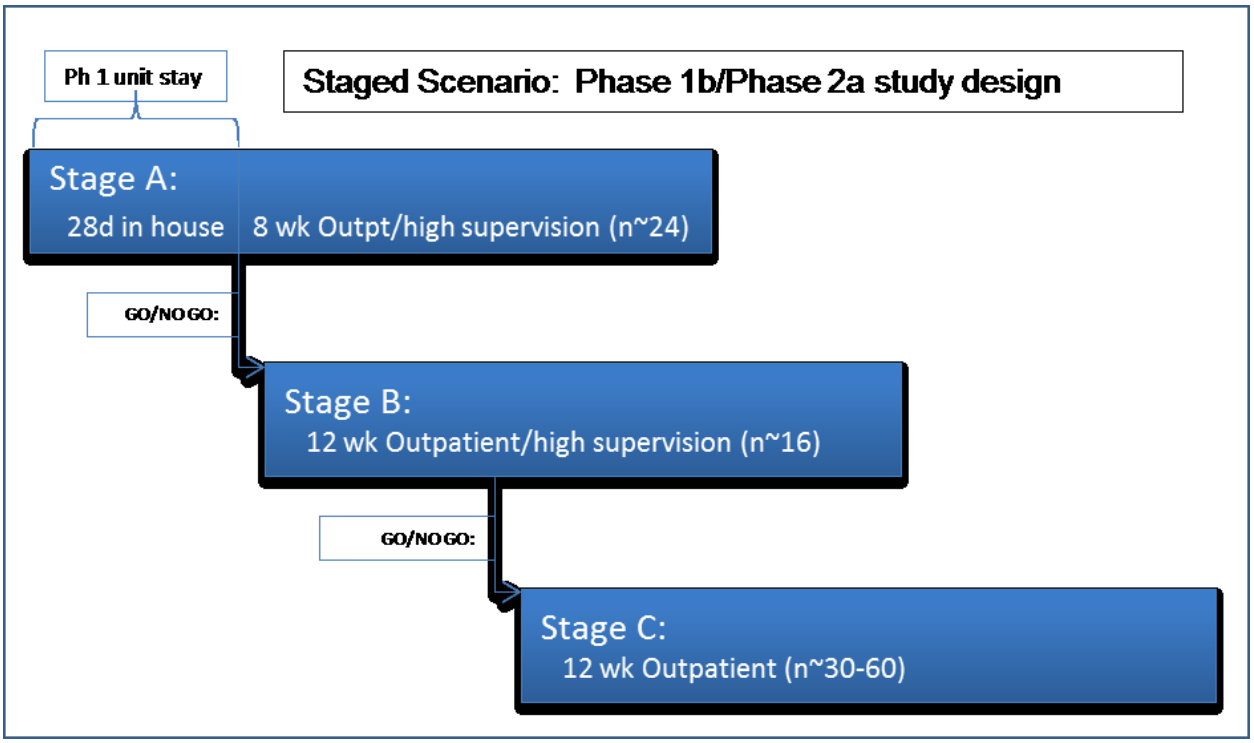
conferring a severe obesity phenotype	• Percent change in body fat mass. • Glucose parameters: fasting glucose, glycated hemoglobin (HbA1c), oral glucose tolerance test (OGTT) with focus on parameters of insulin sensitivity. • Waist circumference. • During withdrawal from drug: reversal of weight and hunger reduction during the double-blind placebo-controlled withdrawal period.				

5.2. Review Strategy

My review focused on studies pertinent to the sought indication. For this purpose, the evaluation of efficacy relied primarily on studies RM-493-012 (Study 012) and RM-493-015 (Study 015). Although study RM-493-011 (Study 011) also included POMC and LEPR deficiency patients, subjects in this study did not have relevant data based on duration of exposure and dosing. Although ultimately my goal has been to characterize the safety and profile of Setmelanotide in POMC/PCSK1 and LEPR deficiency obesity population as a whole, a case-by-case review was performed due the unique phenotypic and clinical characteristics of the study subjects. I also reviewed the submitted results of all studies to familiarize myself with the adverse profile of Setmelanotide, however I identified no additional significant information that was relevant to include in this review.

The only study not presented in section 6 of this review which provided important insight in the adverse event (AE) profile of Setmelanotide was study RM-493-009 (Study 009). The title of the study was "A Staged, Phase 1b/Phase 2a, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety and Efficacy of RM-493, a Melanocortin 4 Receptor (MC4R) Agonist in Obese Patients using a Once or Twice Daily Subcutaneous Injection Formula". Patients who were obese (BMI between 30-40 kg/m_2), but otherwise healthy, were enrolled. This study was planned to be conducted in three sequential stages to account for safety and tolerability. See Figure 3 below.

Figure 3. RM-493-009 Study Design



Overall 99 subjects were enrolled and assigned study treatments within Stages A, B, and C.

Table 2. Subject Disposition, Stages A, B, and C

Stage A	Stage B	Stage C
Enrolled 25 subjects	Enrolled 17 subjects	Enrolled 57 subjects
Treated 25 subjects 19 active/6 placebo	Treated 17 subjects 11 active/6 placebo	Treated 57 subjects 29 active/28 placebo
20 subjects completed	16 completed subjects	47 completed subjects
5 did not complete 3 due to AE/ 1 withdrew consent/ 1 due to 'other' – non-compliance with study visits	1 did not complete due to 'other' – non-compliance with study visits	10 did not complete 3 due to AE/ 7 withdrew consent

The dosing used were 0.75mg BID and 1.5mg QD for stage A, 1.5mg QD in stage B and 2mg QD in stage C.

I selected this study due to the placebo-controlled portion that has similar dose exposure (2mg) to the dose recommended in this application. The safety profile observed (setmelanotide vs placebo) is presented in Table 3 below.

Table 3. Adverse Reactions Occurring in 5% or More of Patients Treated with IMCIVREE and More Frequently than in Placebo in a 12-Week Randomized, Controlled Study

Adverse Reaction	Setmelanotide N=59(%)	Placebo N=40(%)
Skin Hyperpigmentation	47(80%)	3(8%)
Injection Site Reactions	42(71%)	15(30%)
Nausea	32(54%)	5(13%)
Headache	29(50%)	11(28%)
Vomiting	18(31%)	4(10%)
Spontaneous Penile Erection	9(38%)*	0
Diarrhea	16(27%)	4(10%)
Fatigue	13(22%)	3(8%)
Abdominal Pain	10(17%)	2(5%)
Back Pain	8(14%)	0
Disturbance in Sexual Arousal	5(14%)**	0

Sleep Disorder	7(12%)	0
Melanocytic Nevus	4(7%)	0
Alopecia	4(7%)	0
Depression	3(5%)	0

*percent based on number of males
**percent based on number of females

The results of this study allowed me to better interpret and evaluate the safety profile of Setmelanotide in the intended to treat population. A discussion of my interpretation of this data is available in section 8.

6 Review of Relevant Individual Trials Used to Support Efficacy

6.1. RM-493-012

6.1.1. Study Design

Overview and Objective

Title of Study: An open-label, 1-year trial, including a double-blind placebo-controlled withdrawal period, of setmelanotide (RM- 493), a melanocortin 4 receptor (MC4R) agonist, in early onset POMC deficiency obesity due to bi-allelic loss-of -function POMC or PCSK1 genetic mutation.

Trial Design

Study 012 was a multicenter, open-label, Phase 3 pivotal study to assess long-term (1 year) safety and efficacy of setmelanotide in patients with pro-opiomelanocortin (POMC) deficiency obesity (pediatric, adolescents and adults).

The study contained two cohorts of patients: a pivotal cohort and a supplemental cohort.

The maximum allowable dose differed across countries based on feedback from the respective authorities. The US, Canada and UK authorities approved a maximum daily dose of 3.0 mg, while Germany and France authorities initially approved a maximum daily dose of 2.5 mg.

The study began with an initial period (dose titration) lasting 2 to 12 weeks (dependent upon number of dose escalations required to determine an individual's therapeutic dose). During the dose titration, increments of 0.5 mg dose increases were performed at weekly intervals to determine an individual's therapeutic dose, up to the approved maximum dose in the specific country of the participating site (See Table. 4). Thereafter, patients continued active treatment

at their specific optimal therapeutic dose for an additional 10 weeks, for a total combined dosing duration of 12 weeks at the individual patient's therapeutic dose.

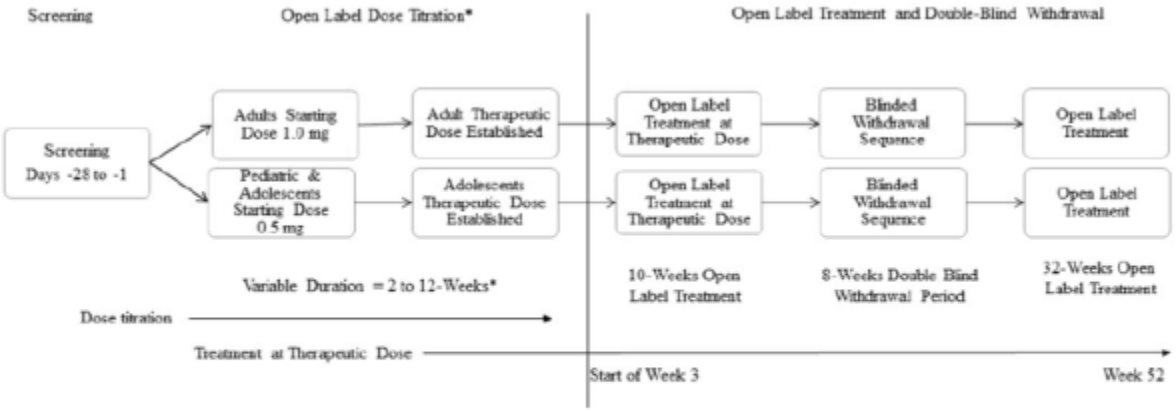
Table 4 Dose Titration Schedule

Dose Titration Week	Adult Dose (mg)	Adolescent Dose (mg)	Pediatric Dose (mg)
1-2	1.0	0.5	0.5
3-4	1.5	1.0	1.0
5-6	2.0	1.5	1.5
7-8	2.5	2.0	2.0
9-10	3.0[a]	2.5	2.5
11-12	NA	3.0[a]	NA

[a] Escalation to 3.0 mg were permitted only if approved by the participating country's competent authority, otherwise the maximum daily dose was 2.5mg.

Patients who achieved at least a 5 kg weight loss (or at least 5% weight loss if baseline body weight was <100 kg) at the end of the Open Label Treatment Period continued into the double-blind, placebo-controlled, withdrawal period lasting 8 weeks, inclusive of a 4-week of placebo treatment period. The clinical protocol indicated that the onset of the placebo period would be variable for each patient in order to mask the actual timing of the withdrawal period; patients, investigators, and investigative sites remained blinded as to when placebo treatment was administered. In actuality, all patients were assigned the same sequence of 4 weeks of active treatment followed by 4 weeks of placebo. Following the withdrawal period, patients went on to complete approximately 1 year of treatment at the therapeutic dose (the primary endpoint defined as 52-weeks after achieving their relative therapeutic dose). It was anticipated that the patient's therapeutic dose, established during the period of dose titration, would be administered throughout the study.

Figure 4 RM-493-012 and RM-493-015 Study Schema



*The last 2 weeks of the open-label dose titration phase in which the therapeutic dose for an individual patient was established was considered the first 2 weeks of open-label treatment. Patients subsequently received an additional 10 weeks of active treatment in the open-label treatment phase for a total combined duration of 12 weeks before transitioning into the double-blind withdrawal phase.

Source: Applicant CSR for RM-493-012

Dose selection:

Previous trials of Setmelanotide demonstrated minimal initial weight loss at doses of 0.25 – 0.5 mg QD, yet meaningful and progressive weight loss with QD doses of 1.0 mg and above. This range of doses was also supported by data in the general obese population. The highest potential dose allowed in dose titration was 3.0 mg.

Toxicology studies in rats and monkeys provided extremely large margins (>150-fold) to human clinical exposures at the 3.0 mg/day dose (in mg/m2 comparisons; greater margins were achieved on a mg/kg basis). Doses up to 10 mg were given in single doses to general obese patients, and the limiting toxicity was nausea (and in some cases vomiting). Otherwise, doses up to 2 mg/day had been administered for up to 12 weeks in healthy obese volunteers prior to this study.

The Schedule of Assessments (SOA) for study screening and dose titration, the 10-week active treatment and 8-week double-blind placebo-controlled withdrawal, and the additional 32-week open-label treatment are depicted in Appendix Table 1.

Objectives:

Primary Objective

- To demonstrate statistically significant and clinically meaningful effects of setmelanotide on percent body weight change in patients with POMC deficiency obesity due to rare bi-allelic or loss-of-function mutations at the end of 1 year of treatment.

Secondary Objectives (to assess the effect of treatment with setmelanotide treatment, over 1 year, on the listed parameters):

- Safety and tolerability of setmelanotide (including BP and HR)
- Hunger for patients ≥12 years of age
- Percent change in body fat mass
- Glucose parameters: fasting glucose, glycated hemoglobin (HbA1c), oral glucose tolerance test (OGTT) with focus on parameters of insulin sensitivity
- Waist circumference
- During withdrawal from drug - reversal of weight and hunger reduction during the double-blind placebo-controlled withdrawal period

Tertiary Objectives (to assess the effect of setmelanotide treatment over 1 year on the following parameters)

- Percent change in total body mass, non-bone lean mass, and bone density.
- Fasting lipid (cholesterol and triglyceride) panel
- Pharmacokinetics of setmelanotide
- C-reactive protein
- Dose response of setmelanotide through titration procedures
- Changes in quality of life and health status

Exploratory Objectives (to assess the effect of setmelanotide treatment over 1 year on the following parameters)

- Hunger for patients between ages 6-11 years.
- Changes in neurocognition in patients 6-16 years of age.
- Change in pubertal development for participants who have yet to reach Tanner Staging V.
- Change in growth and development in patients as assessed by bone age.
- Ambulatory blood pressure measurement (ABPM), skin pigmentation measured by spectrophotometer, energy expenditure, and 24-hour pharmacokinetic profile, only for patients participating in these sub-studies.
- Hormonal, neuroendocrine, metabolic and anti-inflammatory analytes and biomarker assays.
- If identified, a pharmacokinetic/pharmacodynamics (PK/PD) response employing a suitable endocrine biomarker predictive of setmelanotide target engagement, agonism and efficacy through activation of the MC4R.
- If feasible, correlations of bi-allelic or loss-of-function POMC and PCSK1 genetic mutations and POMC deficiency due to diverse allelic variants with the magnitude of setmelanotide efficacy endpoints.

Study Population:

Inclusion Criteria:

1) Bi-allelic, homozygous or compound heterozygous POMC or PCSK1 genes, with the loss-of-function (LOF) variant for each allele conferring a severe obesity phenotype.
2) Age 6 years and above.
3) If adult age ≥18 years, obesity with BMI ≥30 kg/m2; if child or adolescent, obesity with BMI ≥95th percentile for age on growth chart assessment.
4) Able to communicate, to understand and comply with the requirements of the study,
5) Female participants of child-bearing potential agreed to use contraception as outlined in the protocol. Male participants with female partners of childbearing potential agreed to a double barrier method. Male patients were not to donate sperm during and for 90 days following their participation in the study.

Exclusion Criteria:

1) Recent intensive diet and/or exercise regimen with or without the use of weight loss agents including herbal medications, that had resulted in weight loss or weight stabilization. 2) Prior gastric bypass surgery resulting in >10% weight loss durably maintained from the baseline pre-operative weight with no evidence of weight regain.
3) Diagnosis of schizophrenia, bipolar disorder, personality disorder or other Diagnostic and Statistical Manual of Mental Disorders (DSM-III) disorders.
4) A Patient Health Questionnaire-9 (PHQ-9) score of ≥15.
5) Any suicidal ideation of type 4 or 5 on the Columbia Suicide Severity Rating Scale (C-SSRS). Any lifetime history of a suicide attempt, or any suicidal behavior in the last month.
6) Current, severe stable restrictive or obstructive lung disease, evidence of significant heart failure (NYHA Class 3 or greater), or oncologic disease
7) History of significant liver disease or liver injury. The presence of NAFLD was not exclusionary.
8) History or presence of impaired renal function
9) History or close family history (parents or siblings) of skin cancer or melanoma, or patient history of ocular-cutaneous albinism.
10) Significant dermatologic findings relating to melanoma or pre-melanoma skin lesions, determined as part of a screening comprehensive skin evaluation performed by a qualified dermatologist.
11)Not suitable to participate in the study, in the opinion of the Study Investigator.
12) Participation in any clinical study with an investigational drug/device within 3 months prior to the first day of dosing.
13) Significant hypersensitivity to study drug.

14) Inability to comply with QD injection regimen.
15) Patients who had been placed in an institution through an official or court order, as well as those who were dependent on the sponsor, Investigator or study site.

Withdrawal criteria:

1) AEs, which justified cessation of treatment.
2) Non-adherence to study drug regimen or protocol requirements.
3) Non-compliance with instructions or failure to return for follow-up.
4) Failure to demonstrate 5 kg of weight loss (or 5% if baseline body weight <100 kg) at the end of the 10-week open label treatment phase.

All patients that discontinued active treatment prior to completing approximately 1-year of treatment were asked to complete all remaining visits and procedures. In case of withdrawal from the study (withdrawing consent), all adverse events were to have been followed per protocol; any skin adverse experiences were to have been followed, if at all feasible, for approximately 60 to 90 days to confirm near, or complete resolution.

Study Blinding:

This study was open-label, except during the 8-week double-blind, placebo- withdrawal period. The Investigator, study site staff, clinical research organization staff providing site management and CRO Medical Monitor did not have access to the actual treatment sequence being administered during the 8-week double-blind placebo-controlled phase, except in the case of an emergency.

Prior and Concomitant Therapy

When possible, patients were allowed chronic concomitant medications while participating in the study:

Permitted Medications
1) Growth hormone
2) Contraceptives
3) Hormone replacement therapy
4) Anti-hypertensives
5) Statins and other lipid-lowering therapies
6) Thyroxine or other thyroid supplements
7) Other medications commonly used in obese patients: endocrine therapies (e.g., estrogens, Fosamax, hydrocortisone, vitamin and calcium supplements, diabetic therapies including insulin); and other medications (e.g., carnitor, Coenzyme Q10, vitamins, anti-constipation medications, anti-allergic medications).

Prohibited Medications and Substances

1) Low threshold drugs (i.e., anticonvulsants, digoxin, Coumadin, etc.)
2) Medications that could impact the efficacy assessments.
3) Anorectic agents or drugs with anorexia as a non-rare side effect.

Study Endpoints

Primary Endpoint

The primary endpoint stated in the protocol was the proportion of patients in the full analysis set (FAS) who met the ≥10% weight loss threshold (responders) after approximately 1 year of treatment, compared to the proportion from historical data (at most, 5% responders in the null population).

Key Secondary Endpoints

- Mean percent change in body weight from baseline in the Designated User Set (DUS) population
- Mean percent change in weekly average of daily hunger score ('most hunger over the last 24-hours') from baseline in patients ≥12 years of age in the DUS population
- Met responder threshold of ≥25% improvement from baseline in hunger threshold (responders) in the FAS population.

Additional Secondary, Tertiary and Exploratory Endpoints

- The safety and tolerability of treatment with setmelanotide
- Hunger (assessed daily)
- Hunger status and change from baseline at key timepoints
- Body composition (total body weight loss, fat loss, and non-bone lean mass, measured in kg as well as percent change from baseline at the end of 1 year of treatment)
- Glucose parameters (fasting glucose, HbA1c and OGTT)
- Waist circumference
- Hunger response to placebo withdrawal period
- Lipids (fasting cholesterol and triglycerides)
- Health related quality of life (HRQOL) : assessed by using Impact of Weight on Quality of Life-Lite (IWQOL-Lite) and 36-item Short Form Health Survey (SF-36)
- Pediatric HRQOL was assessed with the validated Pediatric Quality of Life Inventory (PedsQL) and the 10-item Short Form Health survey for children (SF-10)
- Changes in pubertal development
- Changes in growth (height, weight and BMI and annual bone maturation)

- Various sub-studies (ABPM, skin color quantification, energy expenditure, and 24-hour PK profile);
- Metabolic and hormonal assays
- Changes in depression/suicidality as assessed by the C- SSRS and Patient Health Questionnaire 9 (PHQ-9)
- PK of setmelanotide in plasma
- Biomarkers and high content proteomic plasma assays predictive of a setmelanotide response, or as a measure of the setmelanotide target engagement were to be potentially evaluated.

Statistical Analysis Plan

Determination of Sample Size

The primary endpoint was the proportion of patients in the Full Analysis Set (FAS) who demonstrated at least 10% weight reduction at ~1 year (10-14 months post baseline) compared to baseline. The primary research hypothesis was that this proportion is at least 5%. The null hypothesis was that this proportion is at most 5%.

Key Analysis Populations

- The FAS population was defined as all patients who received any study drug and had at least one baseline assessment (including those who did and did not demonstrate ≥5 kg weight loss or 5% of body weight [if weight was <100 kg at baseline] over 12-week open label treatment period and proceeded into the double blind, placebo-controlled withdrawal period).
- The DUS (Designated Use Set) population was defined as all patients who received any study drug, demonstrated ≥5 kg weight loss or 5% of body weight (if baseline weight was <100 kg) over 12-week open-label treatment period, and proceeded into the double-blind, placebo-controlled withdrawal period.
- The Completers' Set (CS) population was defined as all patients in the DUS population who demonstrated both ≥5 kg weight loss or 5% of body weight (if baseline weight was <100 kg) over 12-week open-label treatment period and continued in the study on active treatment to complete a full year (approximately) of treatment.
- The Per-Protocol (PP) population was defined as the subset of patients in the FAS population with no major protocol violations.
- The SAS (Safety Analysis Set) population was defined as all patients who received any study drug injections at least one post-dose safety assessment.

Statistical and Analytical Methods and Plans

The primary endpoint was the proportion of patients in the FAS population who achieved at least a 10% weight loss from baseline at approximately 1 year. The null hypothesis was that the proportion was less than or equal to 5% and the alternative hypothesis was that the proportion would be greater than 5%. This comparison was analyzed via the exact binomial test, at one-sided 5% of significance level, and corresponding two-sided 90% CIs were calculated using the exact Clopper-Pearson method.

Key secondary efficacy endpoints were analyzed in the DUS population (percent change from baseline in body weight, "most hunger in the past 24-hours"), and in the FAS population (categorical analysis for a threshold of ≥25% improvement in hunger scores). The first key secondary efficacy endpoint was the percent change from baseline in body weight (kg) at the end of approximately 1 year of treatment in the DUS population, and the second key secondary efficacy endpoint was the mean percent change from baseline in weekly average hunger (using "most hunger over the last 24 hours" daily response) in the DUS population (for patients 12 years of age and older).A linear mixed model repeated measures analysis of variance with a fixed term for time and baseline and a random effect for subjects was used to assess the first and second secondary efficacy endpoint. An unstructured covariance matrix was used to model the expected different variances among the participants. In the event the mixed model did not converge with an unstructured covariance matrix; a compound-symmetric then Toeplitz covariance matrix was employed instead.

The third key secondary endpoint was the proportion of patients in the FAS population who achieved at least a 25% hunger reduction from baseline threshold compared to the null hypothesis that 5% of patients would have achieved this threshold at the end of approximately 1-year of treatment. This was analyzed via the exact binomial test which was planned to test whether the percentage of patients who reach at least 25% hunger improvement was greater than 5%.

Handling of Dropouts or Missing Data

The primary method for handling missing primary/key secondary endpoint data at approximately 1 year first examined the reason for missingness. If unrelated to treatment (e.g.: patient moved), the endpoint would have either been extrapolated using a linear model (y=a+b*study week) based on existing data points or imputed using the longitudinal mixed model for analysis. If the reason for missingness was directly related to treatment (lack of efficacy or an AE), weight change at approximately 1 year was to be conservatively imputed as 0 kg. Likewise, hunger change at approximately 1 year was to be imputed as 0. If less than 3 months of data were available for the supplemental patients at the time of first analysis of the combined cohorts, these patients would not have been imputed and would have been left out of the analysis until more data is available.

For categorical endpoints, all patients not ongoing on test treatment and missing their data at 1 year were considered 'failures,' for example: for the primary analysis, it would have been assumed those missing 1-year data did not achieve at least a 10% weight loss from baseline.

Protocol Amendments

The original protocol (08 June 2016) was amended 13 times. The protocol and amendments were revised to accommodate regional regulations of specific individual participating countries, as appropriate. A summary of substantive changes to the protocol is provided in this section and listed in Appendix Table 4.

Data Quality and Integrity: Sponsor's Assurance

The study was monitored by Rhythm or its designee (both [redacted] (b) (4) provided monitoring for portions of the study). Monitoring included on-site review of source documents/CRFs for completeness and clarity, cross-checking with source documents. Clarification of administrative matters was also performed. The review of medical records was performed in a manner to ensure that patient confidentiality was maintained.
The site monitor ensured that the investigation was conducted according to protocol design and regulatory requirements by frequent communications (letter, telephone, and fax).
Regulatory authorities, the IEC/IRB, and/or Rhythm's clinical quality assurance group or designee may have requested access to all source documents, CRFs, and other study documentation for on-site audit or inspection. Direct access to these documents was guaranteed by the Investigator; the Investigator provided support of these activities throughout the duration of the study.

6.1.2. Study Results

Compliance with Good Clinical Practices

The study was conducted in accordance with the International Council on Harmonization (ICH) for Good Clinical Practice (GCP) and the appropriate regulatory requirement(s). Essential clinical documents were maintained to demonstrate the validity of the study and the integrity of the data collected. Master files were established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

Financial Disclosure

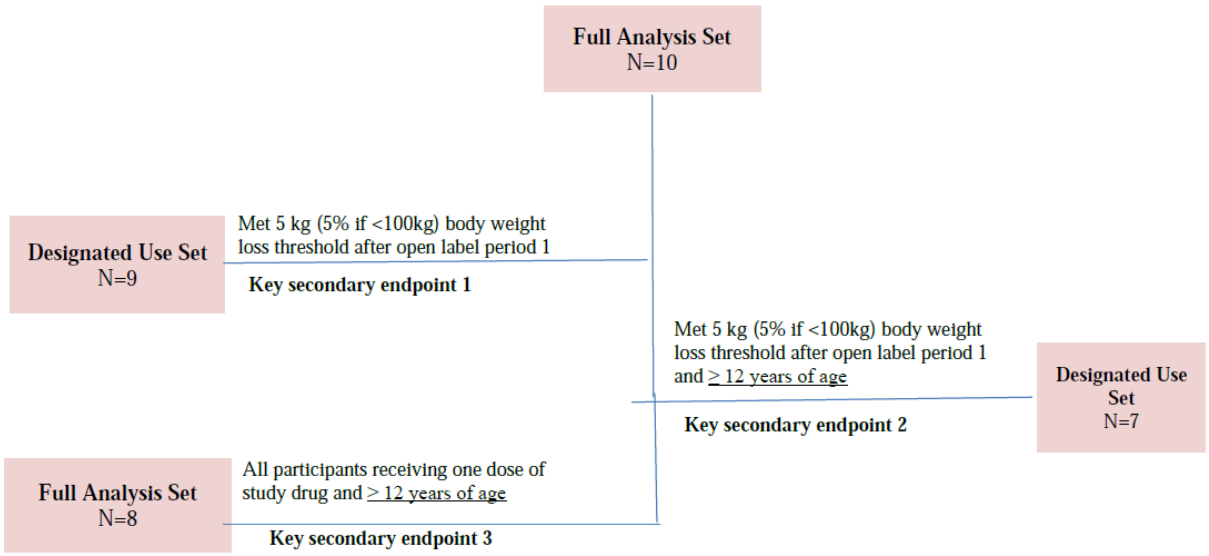
No investigators or sub investigators (study investigators) in Study 012 met the criteria for Financial Interest in the study. Financial Form 3454 was submitted to the NDA.

Patient Disposition

The study report submitted by the Applicant includes data for 14 patients (10 pivotal [9 POMC, 1 PCSK1] and 4 supplemental) who were administered at least 1 setmelanotide dose.

Nine of the 10 pivotal patients completed approximately 1 year of treatment with setmelanotide (1 pivotal patient discontinued treatment due to lack of efficacy). The supplemental patients had not yet completed a year of treatment with setmelanotide.

Figure 5 RM-493-012 Population Disposition



Depending on a site's capabilities and a patient's willingness, there were optional sub-studies to evaluate PK, energy expenditure, skin coloration changes by spectrophotometer (compulsory in Germany and France), and blood pressure/heart rate by ambulatory blood pressure monitoring. It was anticipated that a modest number of patients and sites would participate in each sub-study, and care was taken not to overburden individual patients. For full details of patient enrollment and disposition see Appendix Table 2.

During the dose titration phase and again during the ~32 week open-label treatment phase, pharmacokinetic samples were obtained in order to explore the exposure-response curves for safety and efficacy.

Protocol Violations/Deviations

One supplemental patient withdrew from the study during dose titration due to a protocol violation (b) (6). The subject, (b) (6) with PCSK1 was discontinued from the study due to the variant initially described in *PCSK1* not being corroborated in sequencing Sanger, thus failing to comply with one of the inclusion criteria.
No other protocol violations were recorded for this study.

Patient Demographics

Five (50%) of the 10 pivotal cohort patients were male and 5 (50%) were female. The median age of patients in this cohort was 16.5 years of age (range 11 to 30 years). There were 2

patients <12 years of age. Mean baseline BMI was 40.41 kg/m2 (range 26.2 to 53.3 kg/m2).

Three (3) of the 4 supplemental patients were male and 1 was female. The median age of patients in this cohort was 14.5 years (range 10 to 29 years). There were 2 patients <12 years of age. Mean baseline BMI was 39.04 kg/m2 (range 34.4 to 42.7).

Table 5 Table of Demographic Characteristics

Parameter	Pivotal Cohort (N=10)	Supplemental Cohort (N=4)	Total (N=14)
Age at Enrollment (years)			
n	10	4	14
Mean (SD)	18.4 (6.17)	17.0 (8.76)	18.0 (6.67)
Median	16.5	14.5	16.5
Q1, Q3	15, 22	11, 24	11, 22
Min, Max	11, 30	10, 29	10, 30
Age Categories, n (%)			
< 12 years	2 (20.0)	2 (50.0)	4 (28.6)
≥ 12 years	8 (80.0)	2 (50.0)	10 (71.4)
Sex, n (%)			
Male	5 (50.0)	3 (75.0)	8 (57.1)
Female	5 (50.0)	1 (25.0)	6 (42.9)
Race, n (%)			
White	7 (70.0)	1 (25.0)	8 (57.1)
Other	3 (30.0)	3 (75.0)	6 (42.9)
Arab	1 (10.0)	0	1 (7.1)
Moroccan	1 (10.0)	0	1 (7.1)
NA	1 (10.0)	0	1 (7.1)
Not Reported	0	1 (25.0)	1 (7.1)
Turkish	0	2 (50.0)	2 (14.3)
Ethnicity, n (%)			
Hispanic or Latino	1 (10.0)	1 (25.0)	2 (14.3)
Not Hispanic or Latino	8 (80.0)	2 (50.0)	10 (71.4)
Unknown	1 (10.0)	1 (25.0)	2 (14.3)
Country, n (%)			
United Kingdom	0	0	0
United States	1 (10.0)	0	1 (7.1)
France	1 (10.0)	1 (5.0)	2 (14.3)
Germany	7 (70.0)	0	7 (50.0)
Canada	1 (10.0)	0	1 (7.1)

Spain	0	1 (25.0)	1 (7.1)
Belgium	0	2 (50.0)	2 (14.3)
Gene Type, n (%)			
POMC	9 (90.0)	3 (75.0)	12 (85.7)
PCSK1	1 (10.0)	1 (25.0)	2 (14.3)
Weight (kg)			
n	10	4	14
Mean (SD)	118.7 (37.5)	106.5 (22.8)	115.2 (33.6)
Median	114.950	102.250	114.550
Q1, Q3	106.30, 139.10	92.08, 121.00	100.50, 138.00
Min, Max	55.87, 186.73	83.67, 138.00	55.87, 186.73
Height (cm)			
n	10	4	14
Mean (SD)	169.6 (13.96)	164.5 (11.79)	168.1 (13.14)
Median	170.0	160.5	168.0
Q1, Q3	159, 175	156, 173	158, 175
Min, Max	145, 195	156, 181	145, 195
BMI (kg/m2)			
n	10	4	14
Mean (SD)	40.41 (9.048)	39.04 (4.058)	40.02 (7.803)
Median	40.99	39.52	40.76
Q1, Q3	33.8, 49.1	35.6, 42.4	34.4, 43.7
Min, Max	26.6, 53.3	34.4, 42.7	26.6, 53.3
Waist Circumference (cm)			
n	10	4	14
Mean (SD)	121.80 (18.955)	116.58 (12.969)	120.31 (17.133)
Median	122.50	115.65	121.50
Q1, Q3	112.0, 128.0	106.2, 127.0	109.3, 128.0
Min, Max	86.0, 150.0	103.0, 132.0	86.0, 150.0

Note: Percentage based on the number of subjects in SAS population.
BMI calculated as weight (kg) / [height (m)]2
Source: Applicant's CSR: Table 14.1.1.2, Listing 16.1.2.7. Reviewer confirmed by ADMH and ADSL datasets analyses.

Table 6 Subject level comorbidities

Patient	Age (years)	Comorbidities
(b) (6)	(b) (6)	Hypertriglyceridemia, spinal disc herniation
		Insulin resistance, arterial hypertension, QT prolongation, steatosis hepatitis, and bone defects of both legs (requiring multiple surgeries)
		Bronchial asthma, orthopedic issues of lower extremities, and Blount's disease
		Elongation of QT interval
		Increased blood pressure, fatty liver, and gastric bypass surgery
		Sleep apnea, shortness of breath, increased blood pressure, mitral valve insufficiency, hepatomegaly, hyperlordosis, pes planovalgus, and genua valga
		Hypercholesterolemia, hypertriglyceridemia, and hepatic steatosis
		Sleep apnea syndrome and surgical complications experienced following various bariatric surgical procedures (gastric balloon, sleeve, and bypass, and duodenal switch) such as abdominal evisceration
		History of 2 cardiac arrests
		Asthma, cough, hypertension, congestive heart failure, history of cardiac arrest, thrombosis, and pectus excavatum.
		Hepatic steatosis and dyslipidemia
		Pleuritis, chronic wheezing, history of pleural puncture, elevation of gamma-glutamyltranspeptidase (GGT), and genu varum.
		History of increased HbA1c and increased GGT and ALT.

Source: Applicant's CSR Listing 16.1.2.2. Reviewer confirmed by CRFs evaluation.

Two subjects had cognitive impairment (b) (6) has a history of depression.

Baseline laboratory data at screening is available in Appendix

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Compliance:

Per Applicant's CSR, all used study drug was collected to assess compliance with the protocol. Patients and/or caretakers were required to maintain a study drug diary to further monitor compliance. The time of dosing was recorded in the patient diary.
If a patient did not receive the entire dose of study drug, the amount administered was to be recorded. In addition, the reason(s) for this partial dose was to be recorded in source documents and the CRF.

The Applicant did not provide a compliance assessment in the CSR, however the individual compliance diaries were available. On review of these diaries compliance overall is near 100%. Only 3 subjects have missing doses, Subjects (b) (6) and (b) (6) have one missing dose each. Subject (b) (6) has 6 missing doses, the majority during the titration period and coincide with dose transitions. The last missing dose is on the 41st study day.

Concomitant medications:

The most common concomitant medications were hydrocortisone (9 out of 14 subjects), levothyroxine (5 out of 14 subjects), antihypertensives (3 out of 14 subjects). Details of the prior and concomitant medications are available in Applicant's CSR Table 14.1.1.5.

Efficacy Results – Primary Endpoint

Review of the submitted data shows that, overall, Setmelanotide demonstrated substantial weight loss in POMC subjects with obesity.

Primary endpoint: Proportion of Patients with 10% Body Weight Loss After 1 Year

The primary endpoint was met, with 8 out of 10 (80%, 95% CI: 44.4%, 97.5%) of subjects achieving at least 10% weight loss at 1 year. The 90% and 95% confidence intervals (CI) for the proportion of responders were obtained using the Clopper-Pearson (exact) method. Statistical significance was met if the lower bound of the CI larger than 5%. At least 3 responders out of 10 subjects were needed to achieve statistical significance.

The comparator was a historical reference rate of 5% of responders. Dr. He agreed that the historical response assumption is reasonable, as the data provided by the Applicant suggest that 0% of POMC or LEPR patients would be expected to experience at least 10% weight loss in one year without intervention.

This assumption is also supported by the available published literature data. Historically patients with POMC/PCSK1 or LEPR deficiency obesity have progressive weight gain of 7 to 10 kg/year despite weight management attempts. Of the 24 subjects enrolled in the Applicants development program there were only 6 occurrences of more than 10% weight loss in one year

over 315 patient-years of follow up (<2% per patient-year). Five of these 6 occurrences were following bariatric surgery and were not subsequently enrolled in the pivotal trials. Despite the apparent success of the bariatric intervention in a subset of POMC/PCSK1 or LEPR deficiency obesity, historical data suggests relapse after these interventions in most patients.

The FDA statistical review results concluded that the primary endpoint was met.

Two sensitivity analyses were conducted by the statistical reviewer, including a conservative analysis that considered all missing values as non-responders. For Study 12 there was no missing data, therefore no imputations were necessary.

Key Secondary Endpoints:

The key secondary weight-loss endpoint achieved statistical significance per Applicant's analysis which was confirmed by the statistical review. There was a difference between the Applicant's approach to the statistical evaluation of this endpoint when compared to the FDA analysis. The selected population for the Applicant's analysis the DUS population and a linear mixed model was used.

The FDA statistical reviewer used the FAS population and ran an ANCOVA model.

Per this review, mean percent change in body weight from baseline to 1 year was significantly different from 0 in both studies. The estimate of the mean percent reduction in body weight was greater in the Applicant's analysis of the DUS population than in the FDA analysis of the FAS population, which is expected since the DUS population excluded patients who did not experience early weight reduction.

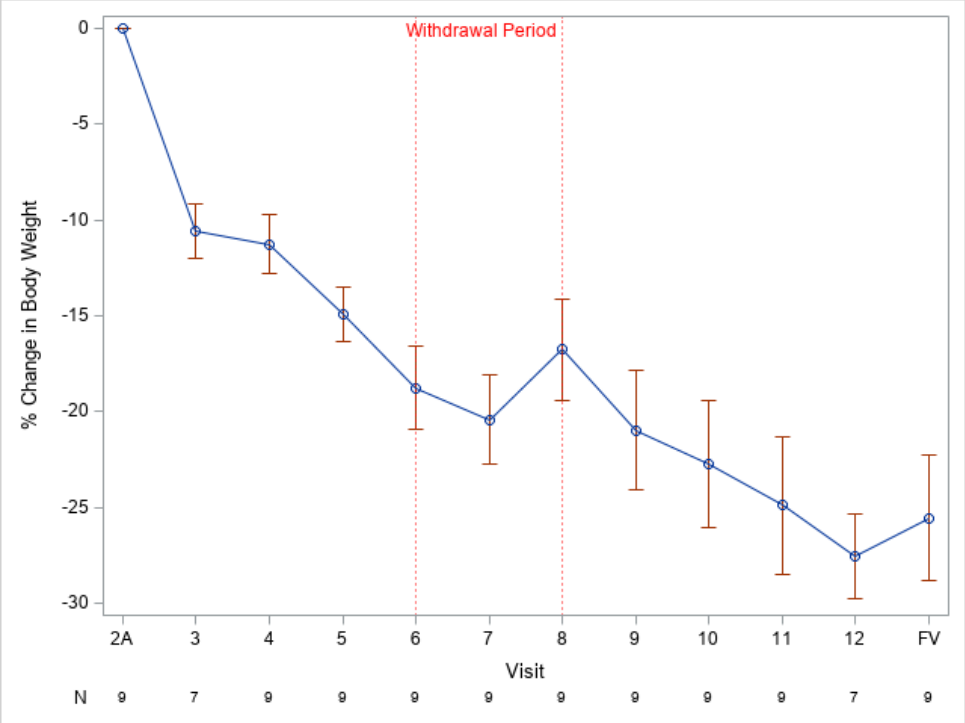
Mean Percent Change in Body Weight from Baseline at ~52 Weeks

On average the mean percent body weight change in the designated population from baseline was -25.6% in the Applicant's analysis.

The FDA statistical analysis concluded that the mean percent change in body weight from baseline at 52 weeks was significantly different from 0 in both the FAS and DUS populations. On average the percent body weight change was -23.1% (95%CI -31.9, -14.4; p<0.0001) in the FAS population and -25.6% (95% CI -31.0, -20.1; p<0.0001) in the DUS population.

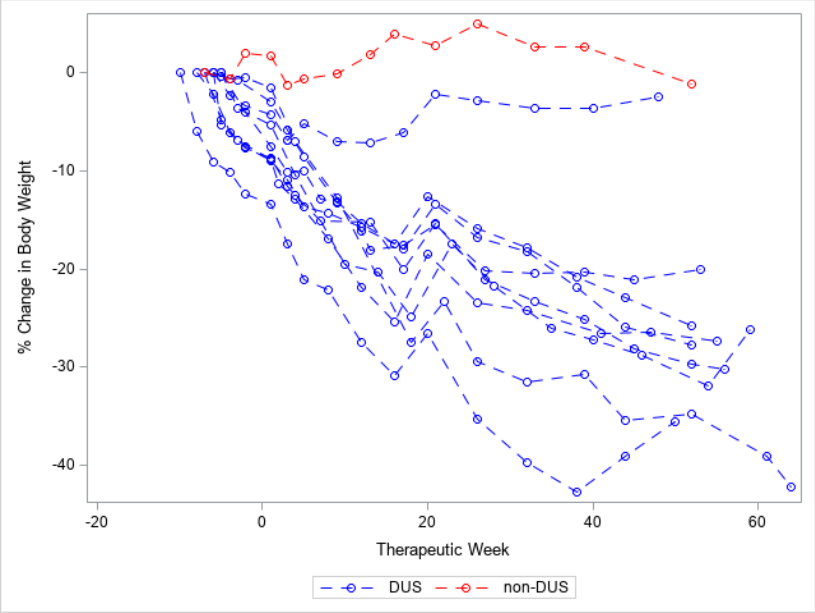
In this population where the expectation is of continuous weight gain any amount of weight loss over one year is likely relevant. Even if we consider parameters applicable to general obesity, where weight loss of 5-10%/year are considered clinically relevant, a weight loss of >10% in the studied population is impressive.

Figure 6 Mean Percent Change in Body Weight from Baseline– DUS



1. Error bars represent standard errors. N represents the number of subjects with observed values.
Source: Statistical Reviewer's Analyses

Figure 7 Percent Change in Body Weight from Baseline in Individual Patients–FAS



Source: Statistical Reviewer's Analyses

Out of the entire cohort there are two subjects enrolled with presumed PCSK1. Subject (b) (6) who was part of the pivotal cohort and subject (b) (6) who was in the supplemental group. Subject (b) (6) was discontinued because of failure of confirmation of mutation with no POMC or PCSK1 variants detected.

The statistical reviewer concluded that the data obtained during the the double-blind withdrawal period provided supportive evidence of the effect of setmelanotide on weight loss in POMC/PCSK1 populations, as it allowed each subject to serve as his or her own control.

Although there was no parallel control arm in this study, the data from the subjects that qualified as responders the withdrawal period was associated with weight gain. Following reintroduction of Setmelanotide after 4 weeks of placebo administration, the overall weight trajectory of the trial subjects resumed a descending trend.

This suggests the weight loss was directly corelated with treatment with setmelanotide and represents a substantial and clinically significant finding, especially in the context of the natural history of the disease.

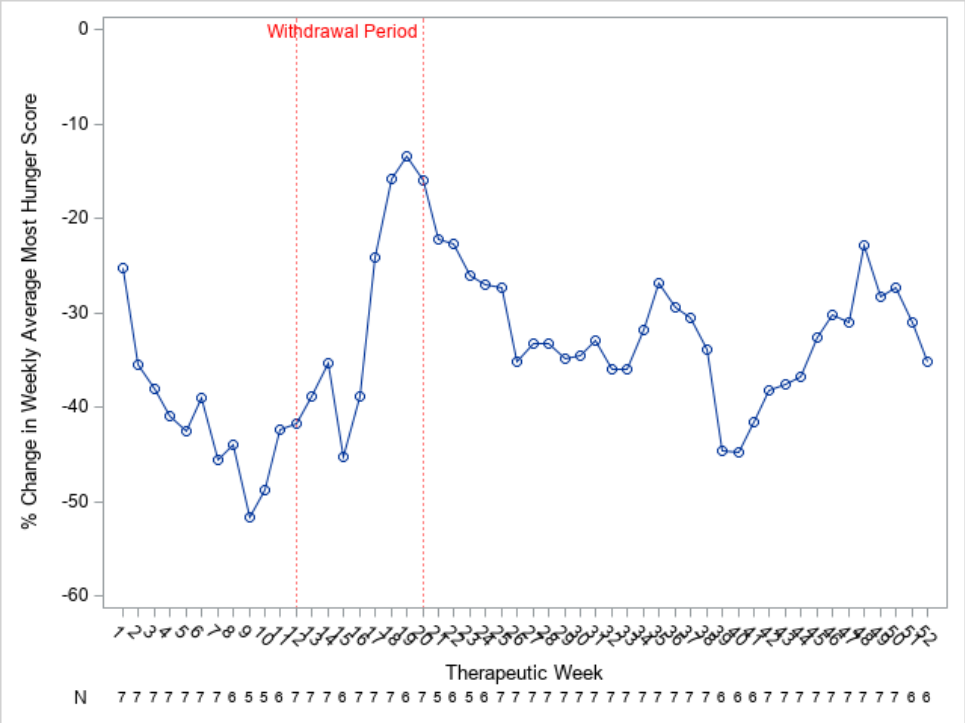
Mean Percent Change in Hunger Score (Worst 'Most' Hunger in 24 Hours) at 52 Weeks

The second key secondary endpoint of this study was to evaluate the mean percent change in hunger scores for patients ≥12 years of age with POMC/PCSK1 deficiency obesity in the DUS Population following 1 year of treatment with setmelanotide. The mean baseline score of the 7 patients ≥12 years of age in the DUS population was 8.1(median 8.0), the mean score at Week 52 following treatment with setmelanotide was 5.8, and the mean score percent change from baseline to Week 52 was -27.1%.

The statistical reviewer's evaluation of the mean percent change in weekly average of daily "most hunger" score from baseline to 1 year concluded that this endpoint was also significantly different from 0 in both FAS and DUS.

The effect of the withdrawal period and reinitiation of treatment with setmelanotide on hunger score was observed in some but not all of the patients in the DUS population. Unlike the gradual decrease in body weight over time, the hunger score measures in individual subjects fluctuated with a high variance, and the trend was less clear in individual patients (graphs now shown). Mean percent change in hunger score did show an obvious increase during the 4-weeks of placebo period. The mean percent change in weekly average of daily 'most hunger' score at 1 year in subjects 12 years and older was -31.2% (95%CI -53.6,-8.7; p=0.007) in the FAS population and -27.1% (95% CI -46.9,-7.2; p=0.009) in the DUS population.

Figure 8 Mean Percent Change in Weekly Average "Most Hunger" Score from Baseline1– DUS; **≥12** Years



1. N represents the number of subjects with observed values.

Source: Statistical Reviewer's Analyses

While these results seem to support that setmelanotide reduces maximal daily hunger in the POMC/PCSK1 population, the COA data is difficult to interpret due to potential measurement challenges related to study design, content validity and other measurement properties, and interpretation of meaningful within-patient change. For details see the COA consult review by Dr. Choudhry.

It is my impression that given the natural history of the disease any reduction in hunger should be viewed as beneficial. However, at this time, the clinical relevance of the metrics used in the PRO is also questionable. The concept of "maximal hunger" may not be the best indicator of satiety and may not adequately capture the effects of Setmelanotide.

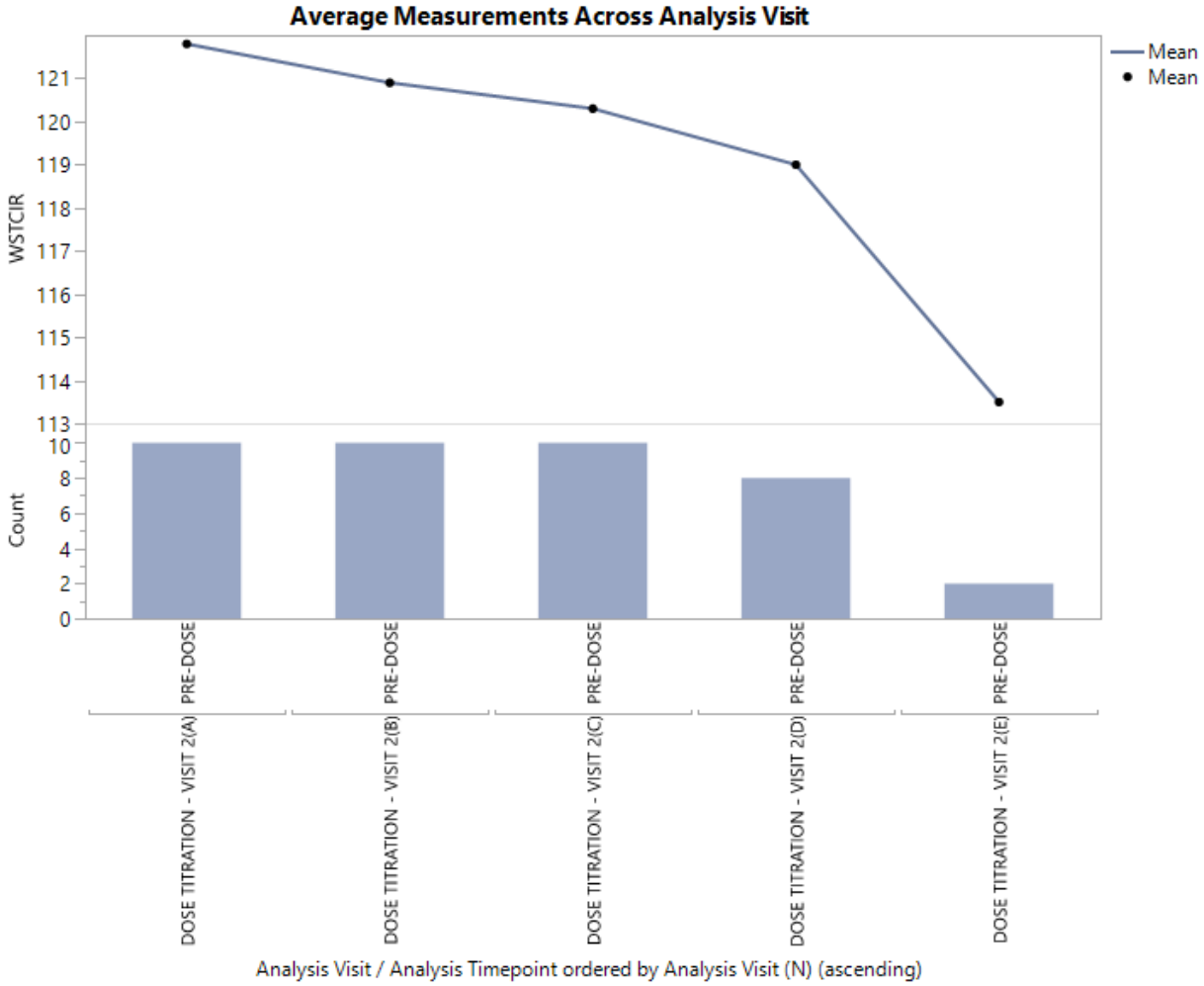
Proportion of Patients Achieving at Least 25% Improvement in Hunger Scores

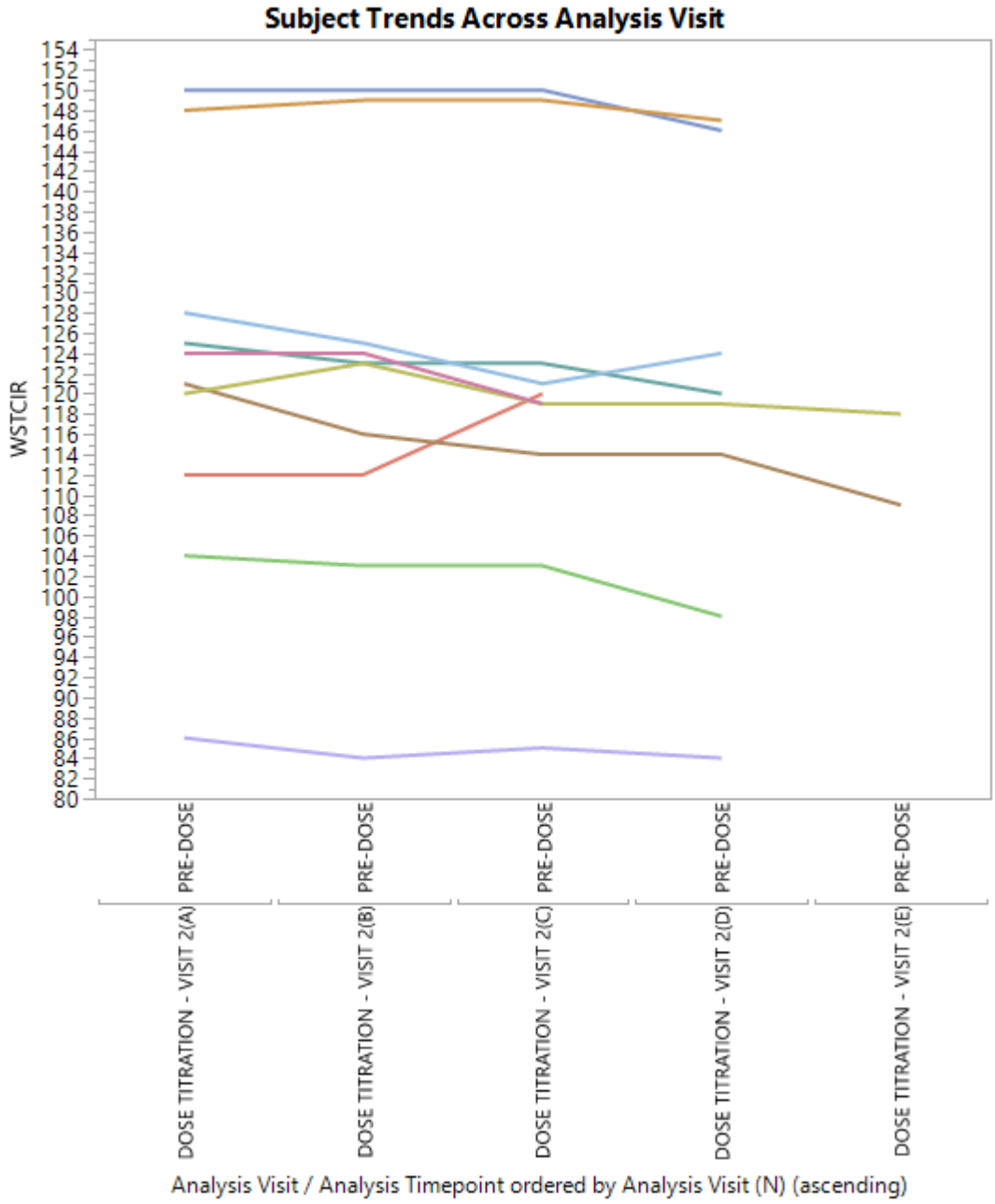
Based on the FDA statistical review 4(50%), of the 8 patients 95%CI 15.7, 84.3: p=0.0004 (from exact binomial test, testing the null hypothesis: proportion =5%) in the FAS Population achieved at least 25% hunger score (worst 'most' hunger in 24 hours) improvement from baseline at Week 52 after treatment with setmelanotide.

Other Secondary, Tertiary, and Exploratory Endpoints

Waist Circumference

Per Applicant's submission, the mean baseline waist circumference in the 9 patients comprising the DUS population was 118.9 cm, the mean waist circumference at Week 52 was 100.5 cm, and the absolute change from baseline at Week 52 was 18.39 cm.
During my analysis I observed that while the average WC seems to substantially decrease the individual variation is less pronounced and the observed decrease in mean WC measurement is artificially enhanced due to missing data towards the end of trial (see figures below).





The current recommended cutoffs that signal CV risk for WC is >88cm in women and >102cm in men. There were no subjects that decreased below these thresholds from baseline to last recorded measurement for me to be able to assign clinical relevance of CV risk reduction.

Waist circumference may be a practical measure of abdominal fat and as an extrapolation of visceral adiposity, however per the current CDC guidance it should be used as a screening tool

rather than a diagnostic of the body fat or health of an individual[7].

Furthermore, The Systematic Evidence Review From The Obesity Expert Panel from 2013 was unable to address issues of the adequacy of current waist circumference cut points for overweight and obesity in comparison to alternative cut points.

Given the limitations of WC measurement in general, beyond a screening tool for CV risk, and the limited data available no clinical significance can be attributed to this endpoint for this trial.

Body Weight – During Placebo Withdrawal Period

After the initial titration and OLE period the subjects identified as responders underwent a placebo withdrawal period of 4 weeks. The withdrawal period was timed around week 16 of the study, and there appeared to be an increase in body weight in all DUS subjects. The mean absolute change in body weight of 8 of the 9 patients comprising the DUS Population was a weight loss of 3.0 kg during treatment with setmelanotide as compared to a mean 5.5 kg weight gain while being administered placebo. The timing of the increase and decrease in body weight matched the starting and ending of the 4-weeks of placebo in the double-blind withdrawal period

Daily Hunger Scores – During Placebo Withdrawal Period

The effect of the withdrawal period and reinitiation of treatment with setmelanotide on hunger score was observed in some but not all the patients in the DUS population. The hunger score measures in individual subjects were variable and the trend was less clear in individual patients and the correlation when compared with the weight data. Mean percent change in hunger score did show an increase during the 4-weeks of placebo period. The mean hunger score (worst 'most' hunger in 24 hours) of 6 of the 7 patients (≥12 years of age) in the DUS Population was 4.9 while being administered setmelanotide and 7.1 while receiving placebo. The mean absolute change in hunger score between the 2 periods was 2.2. Despite numerically trending towards an improvement it is difficult to make a clinical inference of benefit. The variable response among subjects, as well as for each individual, during the withdrawal period makes the clinical reliability of the hunger scoring questionable. Furthermore, with no supporting data for daily hunger scores in the natural history of the disease and the pre-treatment variation in hunger scores in these subjects it is impossible to interpret the relevance of the mean absolute change in hunger score of 2.2 units.

Body Composition

Overall, most of the observed body weight loss was from body fat, 23 kg of the 31 kg lost. Body mass was reduced 27% while body fat was reduced 38%. Overall, there was no loss of bone density and minimal loss in non-bone lean body mass. Refer to Table 7 for details of body composition results.

[7]https://www.cdc.gov/healthyweight/assessing/index.html#:~:text=To%20correctly%20measure%20waist%20circumference,just%20after%20you%20breathe%20out

Table 7 DEXA/BIA Body Mass and Body Fat – Absolute and Percent Change from Baseline - Pivotal Cohort (DUS Population)

Visit	Statistic	Body Mass (g) (N = 9)	Body Fat (g) (N = 9)
Baseline	n	9	9
	Mean (SD)	113278.90 (38778.742)	55255.44 (21088.259)
	Median	113300.00	51200.00
	Q1, Q3	103400.0, 127800.0	47700.0, 66200.0
	Min, Max	54620.1, 186200.0	24884.0, 91900.0
Week 52	n	8	8
	Mean (SD)	77263.94 (17513.334)	30328.34 (11278.019)
	Median	78250.00	25366.35
	Q1, Q3	64090.8, 90200.0	21697.0, 40050.0
	Min, Max	51830.0, 101200.0	19500.0, 48900.0
Absolute Change from Baseline to Week 52 (g)	n	8	8
	Mean (SD)	-26899.83 (13355.972)	-20346.54 (9171.241)
	Median	-30850.00	-23000.00
	Q1, Q3	-35900.0, -20980.0	-26550.0, -16160.5
	Min, Max	-39500.0, -238.6	-29500.0, -1851.3
	LS Mean[a]	-28732.80	-23371.93
	90% CI[a]	(-31973.05, -25492.55)	(-28861.57, -17882.29)
	p-value[a]	<.0001	<.0001
Percent Change from Baseline to Week 52 (%)	n	8	8
	Mean (SD)	-23.90 (10.203)	-38.64 (15.395)
	Median	-26.53	-37.64
	Q1, Q3	-28.0, -23.5	-48.8, -34.7
	Min, Max	-34.9, -0.4	-59.3, -7.4
	LS Mean[b]	-24.47	-41.01
	90% CI[a]	(-28.45, -20.49)	(-50.15, -31.88)
	P-value1	<.0001	<.0001

[a] Model based summary statistic from longitudinal mixed analysis of variance model with fixed effect for week, baseline body mass or body fat and random effect for subject, one sided p-value from model. Note: DUS population consisted of patients who received any injections of study drug, demonstrated ≥5kg weight loss [or 5% of body weight if weight was <100kg at baseline during the 12-week open-label treatment period, and proceeded into the double-blind, placebo-controlled withdrawal period. Source: Applicant's CSR Table19.

Body Mass Index

Absolute and percent change from baseline in BMI was evaluated after 1 year of treatment with setmelanotide. Per the Applicant's analysis, the mean baseline BMI in the 9 pivotal patients comprising the DUS Population was 38.98 kg/m2, and the mean BMI at Week 52 was 27.76 kg/m2. The mean percent change in BMI at Week 52 was -27.82%.

Energy Expenditure

Resting energy expenditure was assessed in 7 patients at screening, visit 6, and visit 13 using indirect calorimetry. Overall, net reduction in resting energy expenditure (REE) was observed at Visits 6 and 13 compared to assessments at screening and consistent with concomitant body weight loss during treatment with setmelanotide. Average percent change in energy expenditure at Visit 13 from baseline was -25.9%.

Patients with POMC/PCSK1 or LEPR may have a decreased baseline resting energy expenditure. When activating the MC4R it is expected to experience an increase in energy expenditure. This was demonstrated in a short-term administration of Setmelanotide in 12 healthy obese subjects where increased resting energy expenditure and shifted substrate oxidation to fat were observed. This may suggest a peripheral effect of Setmelanotide of increased resting metabolic rate contributing to the weight loss. REE is closely dependent on body mass which likely explains the decrease in REE observed during this trial.

Metabolic Profile

Generally, patients with increased fasting glucose or elevated HbA1c levels at baseline or screening tended towards improved fasting glucose and lower HbA1c levels during treatment with setmelanotide.

Lipid profile data typically trended toward improvement with increases in HDL cholesterol and decreases in triglycerides concentrations as body weight decreased during treatment with setmelanotide.

Refer to Section 7.1.2 of this review for detailed discussion of metabolic endpoints.

Review process:

Because of the small sample size, the rarity of the disease and heterogenicity of the study population my review approach was to assess efficacy at an individual level first. Below, see a discussion of the primary and secondary efficacy discussion at the subject level in the context of the subject's medical history and assessment during the study.

Subject (b) (6)

The patient is a (b) (6) from (b) (6) diagnosed with severe obesity and ACTH deficiency early in infancy. (b) (6) was diagnosed with POMC deficiency at 6 years of age. The patient was described as having (b) (6) The patient's prior medical history included episodes of ECG abnormalities (Sig III Type, negative P wave in III), cerebral seizures, hypertriglyceridemia, and episodic depression.

Additional ongoing medical conditions at the time of enrollment included dermatofibroma, acne vulgaris, ephelides (freckles), hyperkeratosis of the back and hands, and folliculitis. In addition, the patient had comorbid conditions affected by severe obesity that included hypertriglyceridemia and spinal disc herniation.

At study enrollment, the patient was receiving medications to treat hypothyroidism and ACTH deficiency, levothyroxine and hydrocortisone, respectively. These medications were administered throughout the study. In addition, the patient received multi vitamins for vitamin deficiency and ibuprofen for right foot pain as needed during the study.

Summary Clinical and Laboratory Data:

Parameter	Screening (or first recorded)	End of study
Weight (kg)	186.7	107.7
BMI (kg/m2)	49.1	18.04
HR (bpm)	81	57.3
Blood pressure mmHg	116/73	103.7/64
Waist Circumference (cm)	150	110
Weekly Hunger Scores (24h)	6	3.2
Fasting Glucose (mmol/L)	4.94	4.274
HBA1c (%)	4.9	4.9
Total Cholesterol (mmol/L)	4.4	2.46
HDL	0.96	1.29
LDL	2.12	1.06
Triglycerides	3.14	0.62

There were slightly elevated laboratory measurements at pre-study testing which were not considered clinically significant (serum uric acid [499.6 mmol/L, nl 214.1-487.7], creatine phosphokinase [233 IU/L, nl 0-190], and triglycerides [3.14 mmol/L, nl 0-2.26]). Otherwise, laboratory parameters measured at baseline were within normal limits.

Efficacy Endpoints:

Primary Endpoint: Met ≥10% Weight Loss (see Figure 8)
Key Secondary Endpoints:

- Percent change in body weight from baseline: -34.8%

- Percent change in hunger score* from baseline: -14.3%
- Did not meet ≥25% decrease in hunger score from baseline

Total Treatment

After approximately 60 weeks of treatment at a therapeutic dose of setmelanotide (primary endpoint), the patient's body weight decreased from 184 to 113.7 kg and hunger score decreased from 9.0 to 6.0.

After approximately 70 weeks of treatment with setmelanotide (Visit 2a to Visit 13), this patient achieved a total body weight loss of 79 kg (from 186.7 to 107.7 kg) and hunger score decreased from 7.0 to 5.4.

Figure 9 (b) (6) Weight change and weekly average hunger score

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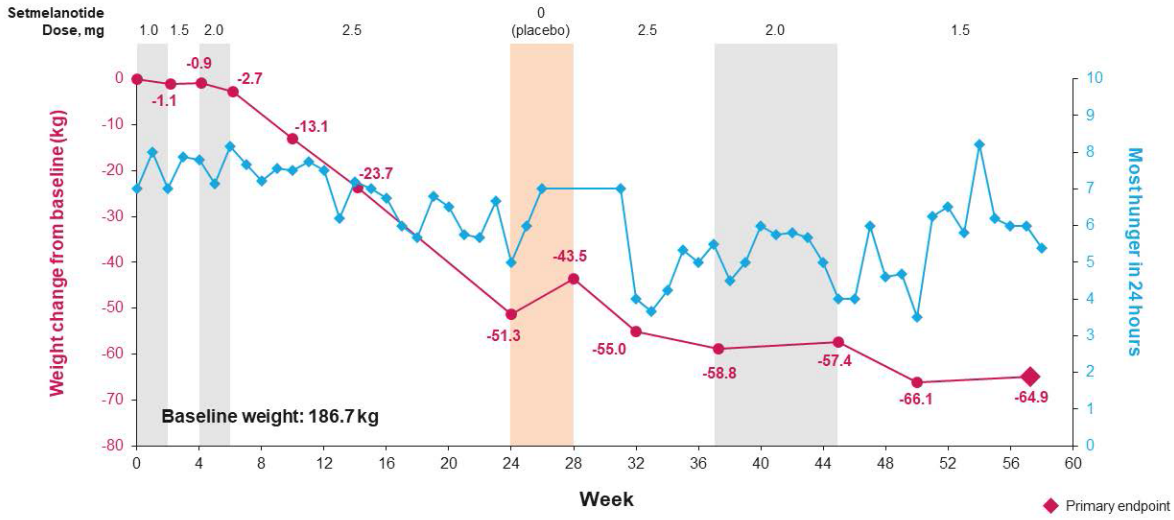
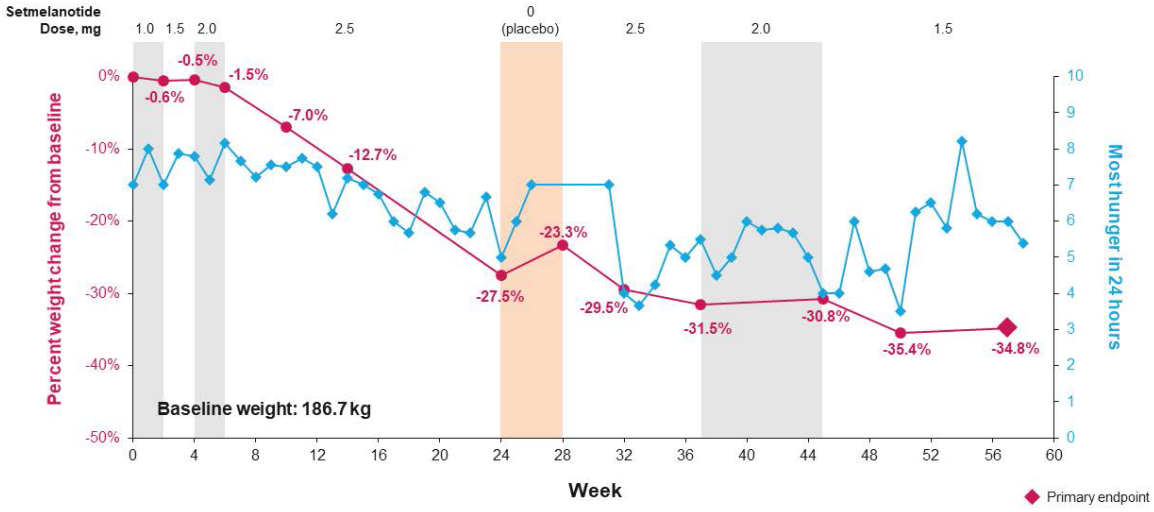




Source: Applicant's CSR page 120/272

Double-Blind, Placebo-controlled Withdrawal Sequence

Following the initial open-label treatment period where the recorded weight loss was of 27.5 kg, the patient was administered placebo for 4 weeks. While receiving placebo for 4 weeks, the patient gained 7.7 kg of weight.
Hunger score data were not available for this patient after receiving placebo for 4 weeks.

Safety Results

Overall, treatment-emergent adverse events (TEAEs) reported for this patient were generally considered mild in intensity and resolved during the study.
The most common (43.4%) TEAEs reported by the patient were injection site reactions (23 of 53), all considered probably related to study drug, mild in intensity, and typically lasting 1 day or less. Other TEAEs considered possibly related to study drug by the Investigator included contractions of abdominal muscles, dry mouth, headache, increased temperature sensitivity, recurrent back pain, restlessness, shivering, syncope, vertigo, and vitamin A&D deficiencies.

Other events of special interest included nausea and vomiting (Day 197, both mild in intensity and lasting 17 days) reported after re-initiation of treatment with setmelanotide following administration of placebo and darkening of skin or hair (mild hyperpigmentation of the skin on Day 62 and new melanocytic nevi on Day 70, both considered ongoing).

During screening, the patient reported a prior medical history of episodic depression. The patient experienced adverse events of tiredness and sadness (Day 311), both considered moderate in intensity with a duration of 100 days and was considered unlikely related to study drug. These TEAEs of tiredness and sadness preceded the TEAE of a depressive episode (Day 352, (b) (6) requiring elective hospitalization, considered severe in intensity, with a duration of 69 days, and considered unrelated to study drug by the investigator. The patient was hospitalized for multimodal (non-pharmacological) psychological therapy that stabilized (b) (6) mood and improved (b) (6) condition.

The C-SSRS responses showed no evidence of suicidal ideation or behavior throughout the study, including during the admission for a depressive episode.

Discussion / Conclusions

Overall, treatment with setmelanotide in this patient with POMC deficiency obesity was generally well tolerated and led to substantial weight loss.

Subject (b) (6)

The patient is a (b) (6), diagnosed with obesity and ACTH deficiency in early infancy. Subsequently, (b) (6) was identified as having the genetic diagnosis of POMC deficiency at approximately 1 year of age.

Past medical history is relevant for insulin resistance, arterial hypertension and QTc prolongation as well as steatosis hepatitis and a history of multiple orthopedic surgical procedures of lower extremities.

Ongoing medical conditions at the time of study enrollment included, genua vara, lower back pain, scoliosis, intellectual disability, melanocytic nevi, and tinea pedis.

At the time of study enrollment, the patient was receiving treatment for ACTH deficiency (hydrocortisone), insulin resistance (metformin), nutritional supplementation (supradyn), and arterial hypertension (ramipril and amlodipine) (b) (6) continued to receive these treatments during treatment with setmelanotide. The patient was hospitalized for treatment of pneumonia and pleural effusion. (b) (6) received inhalation therapy, antibiotics, and increased hydrocortisone

treatment. (b) (6) was discharged from the hospital after 6 days. At the final study visit 6 weeks later, the patient was fully recovered without sequelae.

Liver function laboratory measurements (ALT, AST, and GGT) were elevated at pre-study and considered clinically significant but decreased to within normal limits by approximately 18 weeks of treatment and remained within normal limits for the duration of the study.

Summary Clinical and Laboratory Data:

Parameter	Screening (or first recorded)	End of study
Weight (kg)	139.1	102.7
BMI (kg/m2)	49.88	38.18
HR (bpm)	94.7	82
Blood pressure mmHg	101.7/69.7	101.7/62
Waist Circumference (cm)	112	106
Weekly Hunger Scores (24h)	7.86	3.14
Fasting Glucose (mmol/L)	4.77	4.11
HBA1c (%)	5.1	4.7
Total Cholesterol (mmol/L)	4.63	4.01
HDL	0.7	1.01
LDL	2.67	2.59
Triglycerides	2.68	1.48

This patient had elevated liver function tests (ALT [59 IU/L, nl 0-31], AST [67 IU/L, nl 16-46], GGT [50 IU/L, nl 5-36]) and total bilirubin 1.48 mg/dL [nl 1-1.2] at screening.

Efficacy Results

Primary Endpoint: Met ≥10% Weight Loss (Figure 6)

Key Secondary Endpoints:

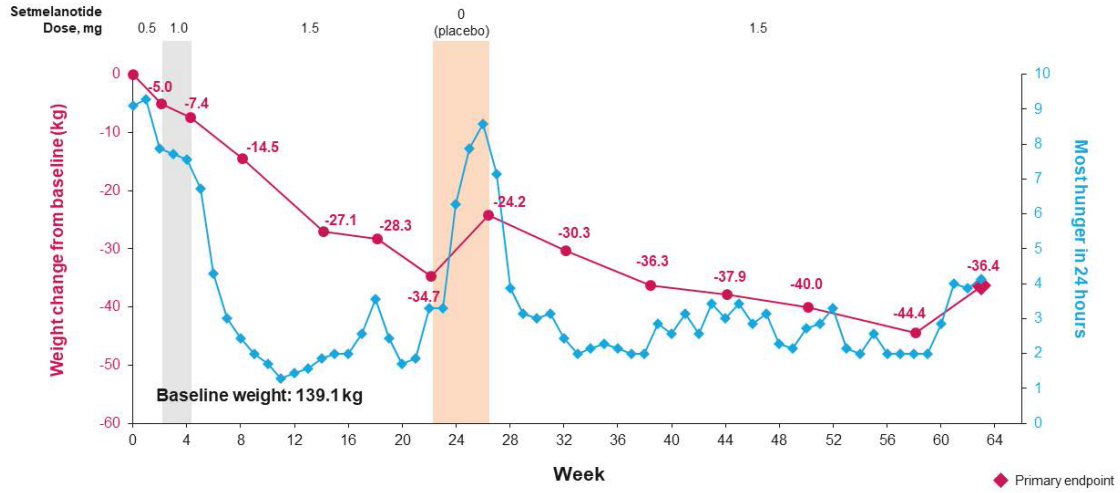
- Percent change in body weight from baseline: -26.2%
- Percent change in hunger score from baseline: -54.7%
- Met ≥25% decrease in hunger score from baseline

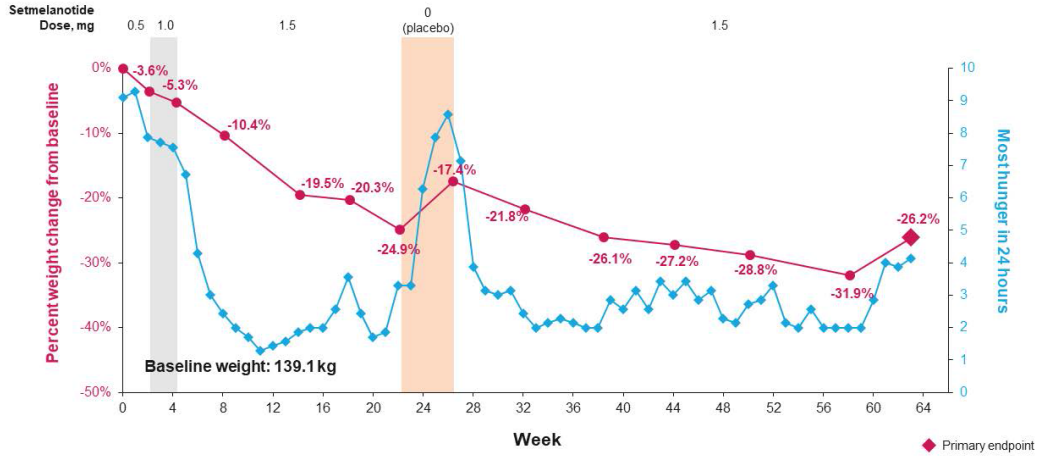
Total Treatment

After approximately 59 weeks of treatment the patient's body weight decreased from 131.7 to 102.7 kg and hunger score decreased from 7.57 to 4.14.

After approximately 63 weeks of overall treatment with setmelanotide there was a total body weight loss of 36.4 kg (139.1 to 102.7 kg), BMI-Z from 4.11 to 3.21, and hunger scores decreased from 9.14 to 4.14.

Figure 10 (b) (6): Weight Change and Weekly Average Hunger Score





Source: Applicant's CSR page 136/272

Double-Blind, Placebo-controlled Withdrawal Sequence

Following the initial open-label treatment period where the recorded weight loss was of 6.4kg (approx. 6 weeks of treatment) and hunger score decreased from 8.57 to 2.43. After receiving placebo for 4 weeks, the patient gained 10.5 kg of body and hunger score increased from 3.29 to 8.57.

Safety Results

The most frequent TEAEs reported by the patient were gastrointestinal in nature (i.e., nausea, vomiting, abdominal pain [13 of 39, 33.3%]) and injection site reactions (i.e., erythema, edema, itching [7 of 39, 17.9%]).

The majority of TEAEs considered possibly related to study drug generally resolved in 1 or 2 days except for TEAEs of hyperpigmentation (ongoing), intermittent abdominal pain (~288 days duration), and alopecia (~203 days duration).

The events of special interest experienced by this patient were nausea, vomiting, ISRs (erythema, edema, itching), and hyperpigmentation (of skin and nevi).

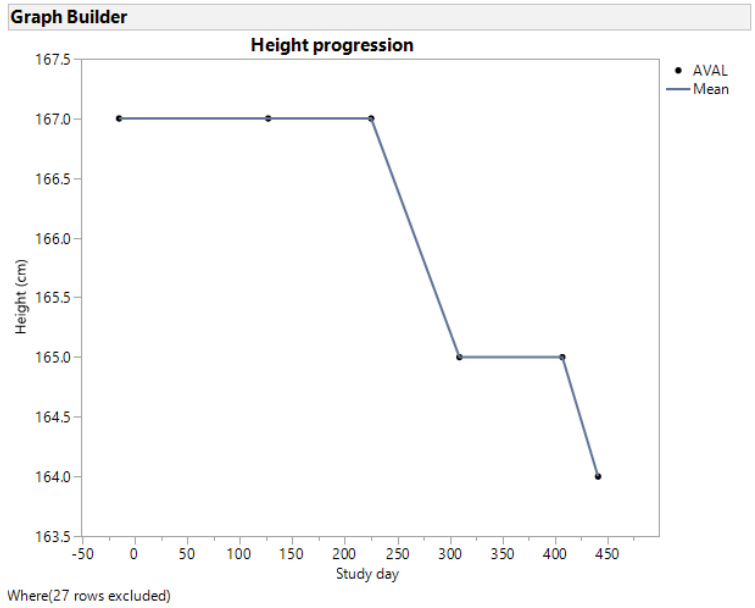
This patient had a serious adverse event, a pleural effusion secondary to pneumonia requiring hospitalization. Serious adverse reporting available indicates (b) (6) was seen at the study clinic for an unscheduled visit with acute back pain, fever, shortness of breath, conjunctival injection, and burning of eyes. Laboratory findings at that time included elevated CRP, leukocytosis, hematuria and proteinuria.

Discussion / Conclusions

Overall, treatment with setmelanotide in this patient with POMC deficiency obesity was well tolerated and led to reduction in hunger scores and substantial weight loss. This patient's lipid profile improved during treatment with setmelanotide, and liver function tests – which were elevated at pre-study – all returned to within normal limits during treatment with setmelanotide.

There is questionable reliability of the height data for this subject, with baseline (and historical) height being higher than the end of study recorded height. This may impact the reliability of the BMI and BMIz assessment, however since the final height is lower, the calculated BMI metrics would be overestimated. Regardless, the patient still achieved primary and secondary endpoints.

Figure 3 (b) (6) Height graph



Subject [redacted] (b) (6)

This patient is a [redacted] (b) (6) with active diagnoses of hypothyroidism, obesity, ACTH deficiency, bronchial asthma, Blount's Disease, and enuresis. (b) (6) was diagnosed with a genetic mutation of POMC deficiency as approximately 2 years of age.

This patient had severe obesity early in life which was well beyond the 95th percentile for age adjusted weight throughout (b) (6) childhood and typically at least ~5kg of weight each year.

Concomitant medications to treat hypothyroidism and ACTH deficiency (levothyroxine, and hydrocortisone, respectively) were continued throughout the study. In addition, the patient received supradyn for vitamin deficiency [redacted] (b) (6) and ibuprofen as needed for right foot pain during the study

Summary Clinical and Laboratory Data:

Parameter	Screening (or first recorded)	End of study
Weight (kg)	106.3	74.2
BMI (kg/m2)	42.58	26.29
HR (bpm)	67	67
Blood pressure mmHg	110.7/63	106.7/66.3
Waist Circumference (cm)	125	103
Weekly Hunger Scores (24h)	7	4.14
Fasting Glucose (mmol/L)	4.05	4.33
HBA1c (%)	5.3	5
Total Cholesterol (mmol/L)	4.91	4.03
HDL	1.6	1.58
LDL	3.28	2.61

Triglycerides	0.72	0.55

At screening, the patient's height was 158 cm (10th percentile); (b) (6) grew a total of 10 cm while participating in the study with 7 cm of growth occurring during the first year in the study, attaining a stature at the 25th percentile. BMI-Z decreased from 3.68 pre-study to 1.59 at the 1-year end of study visit.

Safety laboratory measurements during screening that were outside the normal ranges but were deemed to be without clinical significance were creatinine 43.3 umol/L [nl 50.3-76.9] and lymphocytes 48% [nl 20-47].

Efficacy Results

Primary Endpoint: Met ≥10% Weight Loss

Key Secondary Endpoints:

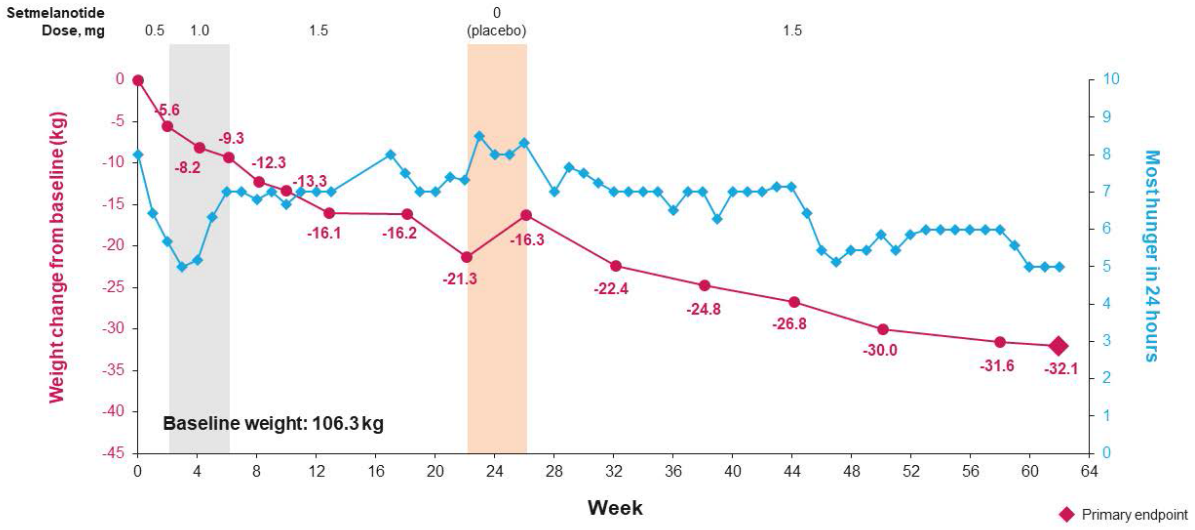
- Percent change in body weight from baseline: -30.2%
- Percent change in hunger score from baseline: -37.5%
- Met ≥25% decrease in hunger score from baseline

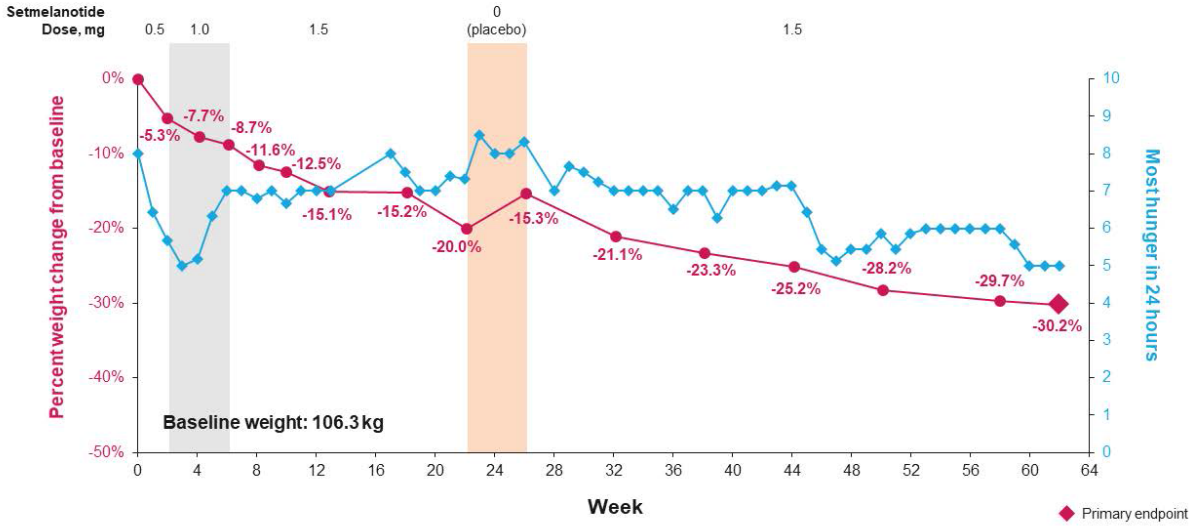
Total Treatment

After approximately 56 weeks of treatment at the therapeutic dose of setmelanotide (from Visit 2d to Visit 13), the patient lost 22.8 kg of body weight (from 97.0 to 74.2 kg) and hunger scores decreased from 7.0 to 5.0.

After approximately 62 weeks of overall treatment with setmelanotide (from Visit 2a to 13), this patient achieved a total body weight loss of 32.1 kg (from 106.3 to 74.2 kg). This patient's BMI-Z scored decreased from 3.68 to 1.59 and hunger scores decreased from 8.0 to 5.0.

Figure 4 (b) (6): Weight Change and Weekly Average Hunger Score





Source: Applicant's CSR page 149/272

Double-Blind, Placebo-controlled Withdrawal Sequence

During the total 12-week administration of setmelanotide at the 1.5 mg daily dose level, the patient experienced a weight loss of 6.9 kg. Hunger scores ranged between6.7 to 7.5 compared to baseline (8.0). After receiving placebo over 4 weeks, the patient gained 5.0 kg and hunger scores returned to near baseline levels (8.33). After reinitiating setmelanotide 1.5 mg daily during the first 6 weeks of the second open-label treatment period, the patient lost 6.1 kg of weight and hunger scores decreased from 8.33 to 7.

Safety Results

The most common TEAEs reported were injection site reactions (ISRs); eighteen (18) of 42 TEAEs reported (42.8%) were ISRs, all considered probably related to study drug, mild in intensity, and typically lasting 1 day or less.

Other TEAEs considered possibly related to study drug by the Investigator included the following: hyperpigmentation (injection site, skin, nevi), nausea, vomiting, dry mouth, dizziness, and punctiform hypopigmentation of the skin. There were no serious adverse events (SAEs) reported for this patient.

Discussion / Conclusions

Overall, treatment with setmelanotide in this patient was well tolerated and led to a decrease in hunger and substantial weight loss.

Subject (b) (6)

This is a (b) (6), with the genetic diagnosis of POMC deficiency made at approximately 5 years of age. (b) (6) was diagnosed with obesity and ACTH deficiency early in infancy and later diagnosed with hypothyroidism. The patient's medical history included a history of a seizure, and elongation of QT interval [QT 30 ms and QTc[E] 436 ms].

Concomitant medications were levothyroxine and hydrocortisone. In addition, the patient was treated with xylometazoline dexpanthenol nasal spray for approximately one week for an upper respiratory infection while receiving treatment with setmelanotide.

Summary Clinical and Laboratory Data:

Parameter	Screening (or first recorded)	End of study
Weight (kg)	114.7	73.9
BMI (kg/m2)	37.5	22.3
HR (bpm)	86	72
Blood pressure mmHg	117.7/78	111/79.7
Waist Circumference (cm)	121	95
Weekly Hunger Scores (24h)	5.71	5
Fasting Glucose (mmol/L)	5.11	4.5
HBA1c (%)	5.5	5.1

Total Cholesterol (mmol/L)	3.65	4.42
HDL	0.7	1.53
LDL	2.56	3.16
Triglycerides	1.14	0.78

There were slightly abnormal laboratory measurements at baseline (ALT [59 IU/L, nl 0-41], BUN [5.712 mmol/L, nl 6.426-16.065], creatinine [45.97 umol/L, nl 61.88-106.08], lactate dehydrogenase [271 IU/L, nl 135-250], phosphate [1.62 mmol/L, nl 0.84-1.45], urate [475.84 umol/L, nl 124.9-452.05], hemoglobin [126 g/L, nl 125-166], lymphocytes [56.0%, nl 20-47], mean platelet volume [12.1 fL, nl 7-12], urine leukocytes [0.041 10/L, nl 0-0.024], and urine occult blood [positive].
LDL cholesterol initially decreased but increased during the later visits of the study (Visit 9-Visit 13).
The subject's height increased from 175 cm to 182 cm.

Efficacy Results

Primary Endpoint: Met ≥10% Weight Loss

Key Secondary Endpoints:

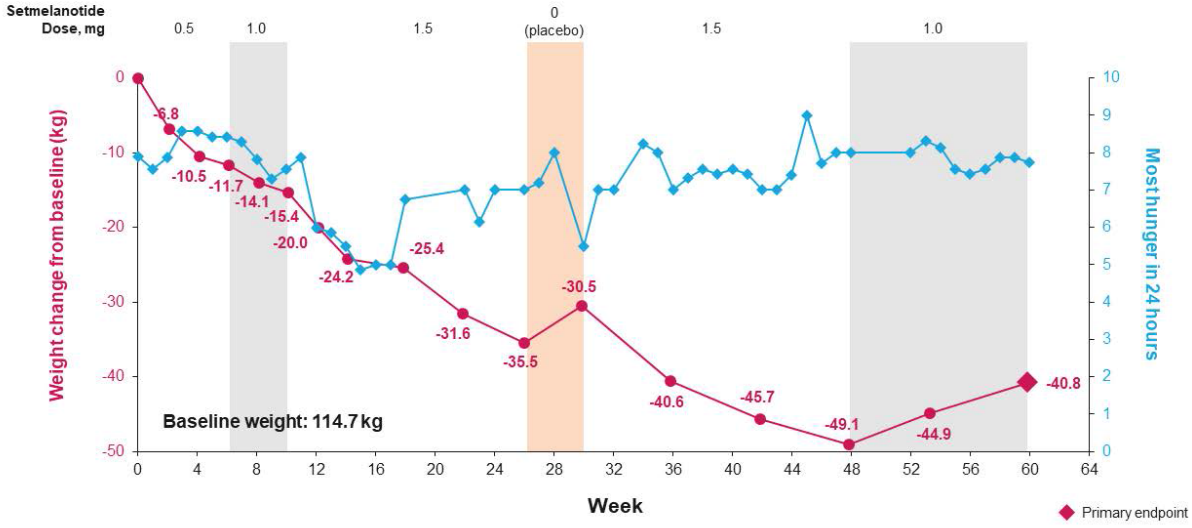
- Percent change in body weight from baseline: -35.6%
- Percent change in hunger score from baseline: -1.4%
- Did not meet ≥25% decrease in hunger score from baseline

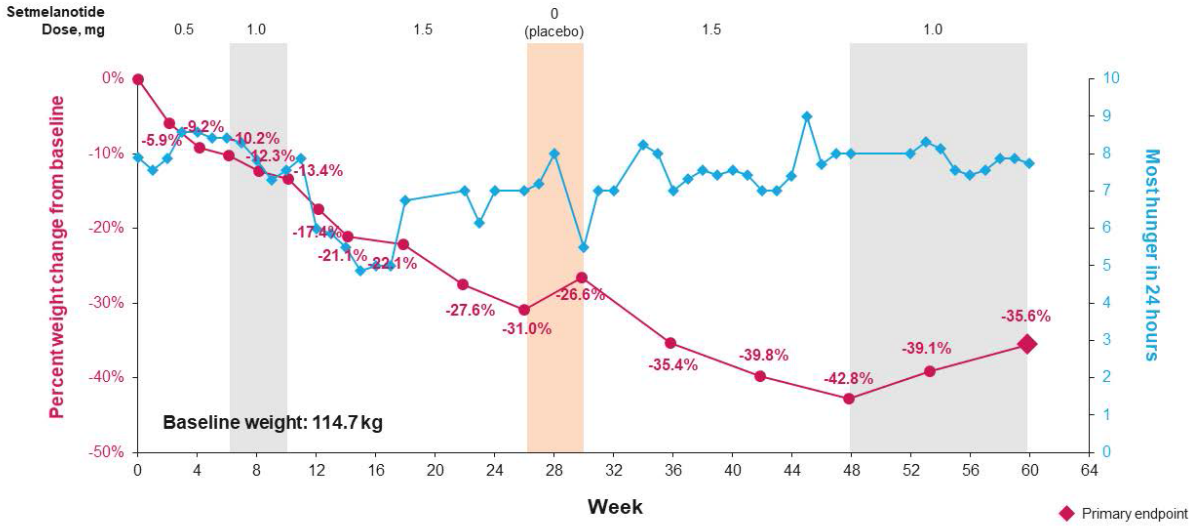
Total Treatment

After approximately 50 weeks the patient's body weight decreased from 99.3 to 73.9 kg and hunger score remain essentially unchanged (from 7.57 to 7.75).
After approximately 60 weeks of overall treatment with setmelantoide the patient lost 40.8 kg of body weight and hunger scores decreased while being administered 1.5 mg daily but increased to pre-study values after the daily dose was decreased to 1.0 mg daily at Visit 11.

At Visit 11, the patient was determined to have reached a normal BMI (from 37.45 kg/m2 [Visit 2a] to 19.8 mg kg/m2[BMI-Z 3.27 to 0.29]) and the Investigator and Sponsor chose to decrease the daily dose of setmelanotide from 1.5 mg to 1.0 mg for the remainder of the study. Over the final weeks of the study (Visit 11-13) following the reduction of daily dose, the patient gained 8.3 kg of body weight, but BMI remained in the normal category. Weekly average hunger scores ranged between 5.5 and 8.3 during this period.

Figure 5 (b) (6): Body Weight Change and Weekly Average Hunger Score





Double-Blind, Placebo-controlled Withdrawal Sequence

During the 16-week administration of setmelanotide at the 1.5 mg daily dose, the patient experienced a weight loss of 20.1 kg (from 99.3 to 79.2 kg). Hunger scores generally ranged between 6 and 7 and during the initial open-label treatment period.
After receiving placebo for 4 weeks, the patient gained 5.0 kg of weight, and hunger scores decreased from 7 to 5.5.
During the first 6 weeks of the second open-label treatment that re-initiated setmelanotide 1.5 mg daily, this patient lost 10.1 kg and hunger scores increased from 5.5 to 7.

Safety Results

The most common TEAEs reported were injection site reactions (ISRs); seven (7) of 21 TEAEs reported by the patient (33.3%) were ISRs, all considered probably related to study drug, mild in intensity, with a duration of 1 day.

Other TEAEs considered possibly related to study drug by the Investigator included hyperpigmentation of skin and nevi, new nevi of lips, elevated bilirubin, and biliary sludge.
Other events of special interest are nausea and vomiting which were considered mild in intensity with a duration of 1 day.

This patient experienced a TEAE of severe hypoglycemia due to acute adrenal insufficiency on (b) (6) (b) (6) requiring hospitalization.
At Visits 6 and 9 laboratory measurements of bilirubin (28.04 umol/L [V6], 33.69 umol/L [V9] uln = 20.52 umol/L) and direct bilirubin (11.12 umol/L [V6], 10.26 umol/L [V9] uln = 5.13) were increased and considered clinically significant by the Investigator. Both bilirubin and total bilirubin levels had returned to normal range by Visit 11.

Discussion / Conclusions

Overall, treatment with setmelanotide in this patient was well tolerated and led to substantial, sustained weight loss resulting in the achievement of a normal BMI. The TEAEs considered related to setmelanotide were generally consistent with those observed in other studies of setmelanotide (i.e., ISRs, skin hyperpigmentation, nausea, vomiting). There was a worsening of the hunger scores, weight and lipid profile in the second OLE period. This seems to coincide to the decrease of setmelanotide dose from 1.5mg to 1.0 mg daily upon achieving normal BMI.

Subject (b) (6):

This is a (b) (6) diagnosed with a genetic mutation of POMC deficiency when (b) (6) was approximately 3 years of age. (b) (6) was diagnosed with obesity and ACTH deficiency early in infancy. The patient's past medical history included iron deficiency anemia, diabetes mellitus type 2, fatty liver, increased blood pressure, adjustment disorder, elevated hs-CRP, hypothyroidism, nevus flammeus, primary amenorrhea, vitamins B12 and D deficiencies, fatty liver and delayed pubertal development. (b) (6) has a history of gastric bypass and was able to lose 19 kg of weight over 6 months (starting weight of 120 kg). (b) (6) was unable to maintain the weight loss, and at screening (b) (6) weighed 117 kg.

Concomitant medications were levothyroxine sodium, prednisone, premens, trisquens and hydrocortisone, fluvoxamine maleate, acarbose and nutritional supplements, supradyn and vitamin D. In addition, the patient received zinc for an upper respiratory infection, as well as domperidone for nausea and omeprazole for morning nausea (both associated with a TEAE) during the study.

Summary Clinical and Laboratory Data:

Parameter	Screening (or first recorded)	End of study
Weight (kg)	115.2	85.5
BMI (kg/m2)	39.4	29.24
HR (bpm)	80.3	87.3
Blood pressure mmHg	122.3/84	112.3/78.7
Waist Circumference (cm)	120	110
Weekly Hunger Scores (max 24h)	7.43	7
Fasting Glucose (mmol/L)	5.05	3.78
HBA1c (%)	5.8	4.8
Total Cholesterol (mmol/L)	4.47	3.49
HDL	1.78	1.42
LDL	2.61	2.1
Triglycerides	2.2	0.99

There were abnormal screening laboratory values (i.e., carbon dioxide [36.5 mmol/L, nl 37-50], potassium 3.5 mmol/L, nl 3.4-4.5], leukocytes [10.57 10/L, nl 3.9-10.5], urine leukocytes [0.025 10/L, nl 0-0.024], urine proteins [positive], and urine specific gravity [1.032, nl 1.01-1.02]. Otherwise, laboratory parameters measured at baseline were within normal limits.

Efficacy Results

Primary Endpoint: Met ≥10% Weight Loss

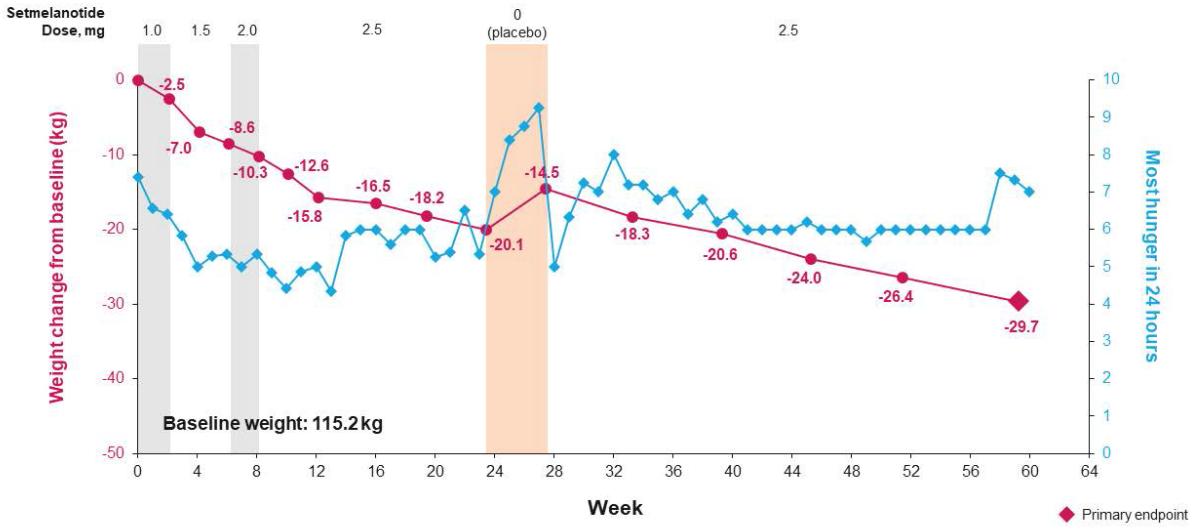
Key Secondary Endpoints:

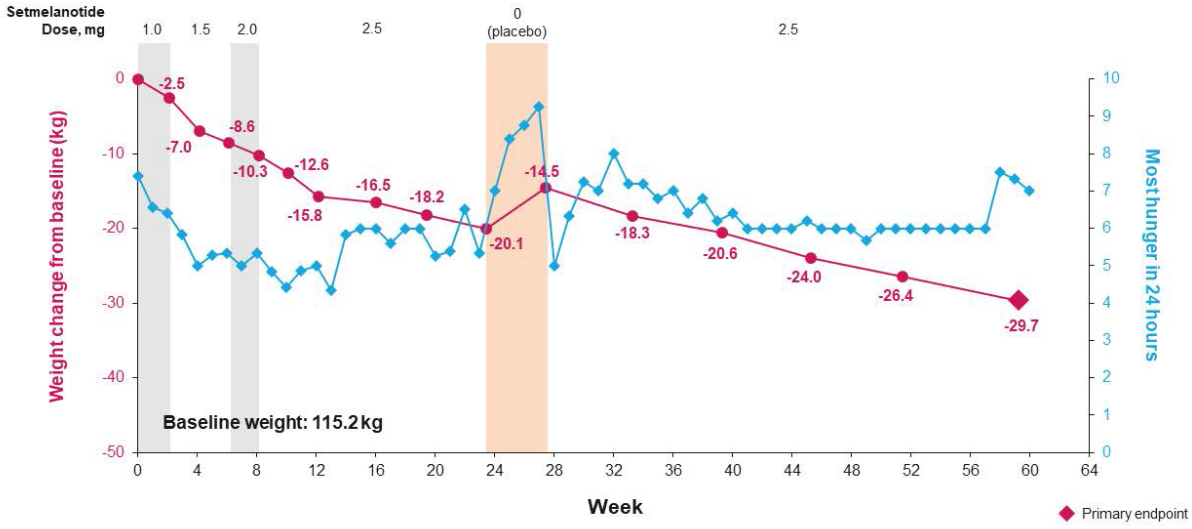
- Percent change in body weight from baseline: -25.9%
- Percent change in hunger score from baseline: - 5.8%
- Did not meet ≥25% decrease in hunger score from baseline

Total Treatment

After approximately 59 weeks of overall treatment with setmelanotide, the patient had achieved a body weight loss of 29.7 kg (from 115.2 to 85.5 kg). Hunger scores were somewhat variable throughout.

Figure 6 (b) (6): Weight Change and Weekly Average Hunger Score





Double-Blind, Placebo-controlled Withdrawal Sequence

The patient achieved the established therapeutic dose level of setmelanotide 2.5 mg daily, during the last 2 weeks of the titration period, and proceeded into the initial open-label treatment period receiving 2.5 mg daily over the next 11 weeks. During this time the patient experienced a weight loss of 9.8 kg (from 104.9 to 95.1 kg). After receiving placebo for 4 weeks, this patient gained 5.6 kg.

Hunger scores were somewhat variable throughout but demonstrated intermittent decreases in hunger.

Safety Results

Overall, treatment-emergent adverse events (TEAEs) reported for this patient were considered mild in intensity and resolved during the study. The most common TEAEs reported were injection site reactions (ISRs); twenty (20) of 44 TEAEs reported by the patient (45.4%) were ISRs.

Other TEAEs considered possibly related to study drug by the Investigator included the following: nausea, headache, fatigue, back pain, shivering and increased olfactory sensitivity.

Other events of special interest experienced by this patient included moderate hyperpigmentation of the skin and nevi (beginning at Day 11), considered ongoing), non-specific active suicidal thoughts (Day 192 to Day 233, and suicidal ideation ('wish to be dead', Day 192, considered ongoing (of note, this patient had a history of adjustment disorder for which (b) (6) was receiving fluvoxamine maleate).

Discussion / Conclusions

Overall, treatment with setmelanotide in this patient was well tolerated and led to substantial, sustained weight loss. The hunger scores were variable and did not show significant improvement. TEAEs of suicidal ideation, hyperpigmentation, olfactory issues were ongoing at the end of study.

The TEAE of suicidal ideation was considered unlikely related to setmelanotide by the investigator in the context of the subject's history of an adjustment disorder.

Subject (b) (6):

This is a (b) (6). A genetic diagnosis of POMC deficiency was first identified approximately 3 years of age. Additional active diagnoses at study enrollment included ACTH deficiency, cognitive disorder, acanthosis nigricans, increased blood pressure, hepatomegaly, lordosis, foot deformity, vitamin D deficiency, aggression, sleep apnea disorder, genua valga, mitral valve incompetence, anemia, obsessive compulsive disorder, dyspnea, and delayed puberty.

Concomitant medications were levothyroxine, hydrocortisone, metformin, ramipril, hydrochlorothiazide, salbutamol, estrogen, (vitamin D, ferrum hausmann, nutritional supplementation (supradyn), and cantharis. These medications were administered during treatment with setmelanotide throughout the study. In addition, the patient received saccaromycea boulardii to treat diarrhea for 2 days in (b) (6)

Summary Clinical and Laboratory Data:

Parameter	Screening (or first recorded)	End of study
Weight (kg)	130.7	95
BMI (kg/m2)	43.7	31.38
HR (bpm)	105.3	82.3
Blood pressure mmHg	118/90.7	116.3/80
Waist Circumference (cm)	123	105
Weekly Hunger Scores (max 24h)	8.29	8
Fasting Glucose (mmol/L)	7.66	3.89
HBA1c (%)	6	5.3
Total Cholesterol (mmol/L)	4.29	4.14
HDL	1.35	1.81
LDL	2.53	2.53
Triglycerides	1.21	0.82

Abnormal labs at screening were: hemoglobin (108 g/L, nl 120-154), mean corpuscular hemoglobin concentration (298 g/L, nl 315-360), mean corpuscular hemoglobin (18.7 pg, nl 26-33), and erythrocyte mean corpuscular volume (62.0 fL, nl 78-96). All other safety laboratory measurements during screening and pre-study were within normal limits or abnormal without clinical significance.

Efficacy Results

Primary Endpoint: Met ≥10% Weight Loss

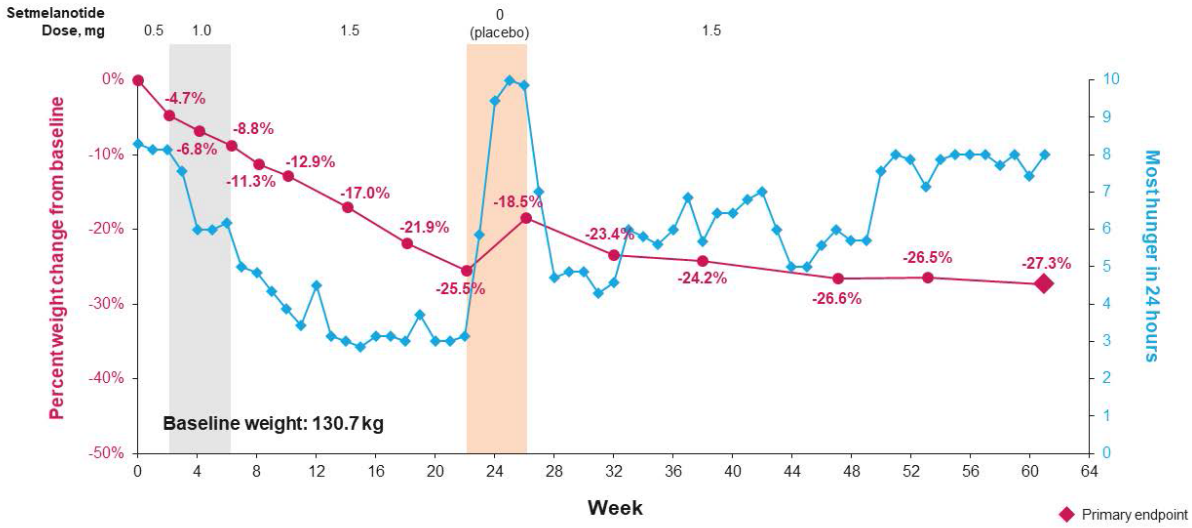
Key Secondary Endpoints:

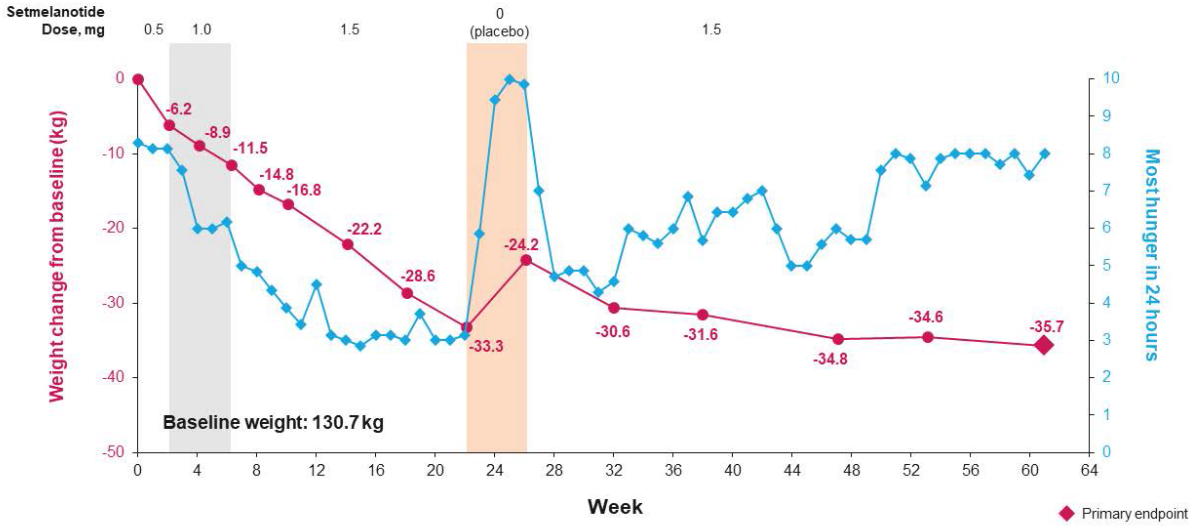
- Percent change in body weight from baseline: -27.3%
- Percent change in hunger score from baseline: -3.5%
- Did not meet ≥25% decrease in hunger score from baseline

Total Treatment

After approximately 55 weeks of treatment at a therapeutic dose of setmelanotide, the patient's body weight decreased from a baseline weight of 130.7 to 95.0 kg. After approximately 61 weeks of treatment with setmelanotide, the patient had achieved a body weight loss of 35.7 kg. Hunger scores had decreased during treatment with setmelanotide (from 8.29 to 3.14) early in the study, however by Visits 12 and 13 had returned to levels similar to baseline (8.0).

Figure 7 (b) (6): Weight Change and Weekly Average Hunger Score





Source: Applicant's CSR page 192/272

Double-Blind, Placebo-controlled Withdrawal Sequence

During the total 14-week administration of setmelanotide at the 1.5 mg daily dose level, the patient experienced a weight loss of 21.8 kg. Following the initial open-label treatment, the patient was administered placebo for 4 weeks. After administration of placebo the patient gained 9.1 kg of body weight and (b) (6) hunger scores increased dramatically from 3.1 to 9.86.

Safety Results

The most common TEAEs reported were injection site reactions (ISRs); nine (9) of 34 TEAEs reported by the patient (26.5%) were ISRs, all considered probably related to study drug, mild in intensity, and typically lasting 1 day or less. Other TEAEs considered possibly related to study drug by the Investigator included the following: hyperpigmentation of the skin, nausea, headache, abdominal pain, and alopecia. The TEAEs of hyperpigmentation of the skin and alopecia remained ongoing at the end of the study.
No SAEs were reported for this patient.

Discussion / Conclusions

Overall, treatment with setmelanotide in this patient was well tolerated and resulted in substantial weight loss. Although there was an initial decrease in hunger scores, by the end of the study period the subject had returned to baseline hunger values.

Subject (b) (6):

This is a (b) (6) with the genetic diagnosis of POMC deficiency identified at 3 years of age. (b) (6) was diagnosed with ACTH deficiency early in infancy. Past medical history is relevant for type I diabetes mellitus, hypercholesterolemia, hypertriglyceridemia, hepatic steatosis, increased C-reactive protein, ephelides (freckles) of face, melanocytic naevus, right knee pain, and systolic heart murmur.
Concomitant medications included hydrocortisone, human and lantus insulin, ibuprofen and naproxen sodium. In addition, the patient received pantoprazole to treat gastritis during the study as needed.

Summary Clinical and Laboratory Data:

Parameter	Screening (or first recorded)	End of study
Weight (kg)	114.4	82.7
BMI (kg/m2)	33.79	24.69
HR (bpm)	83.7	67
Blood pressure (mmHg)	117.7/82.7	121.3/85.7
Waist Circumference (cm)	124	99
Weekly Hunger Scores (max 24h)	8	2.5

Fasting Glucose (mmol/L)	22.7	18.98
HBA1c (%)	10.3	10.6
Total Cholesterol (mmol/L)	5.2	4.27
HDL	0.54	1.06
LDL	2.38	2.69
Triglycerides	6.47	1.19

Efficacy Results

Primary Endpoint: Met ≥10% Weight Loss

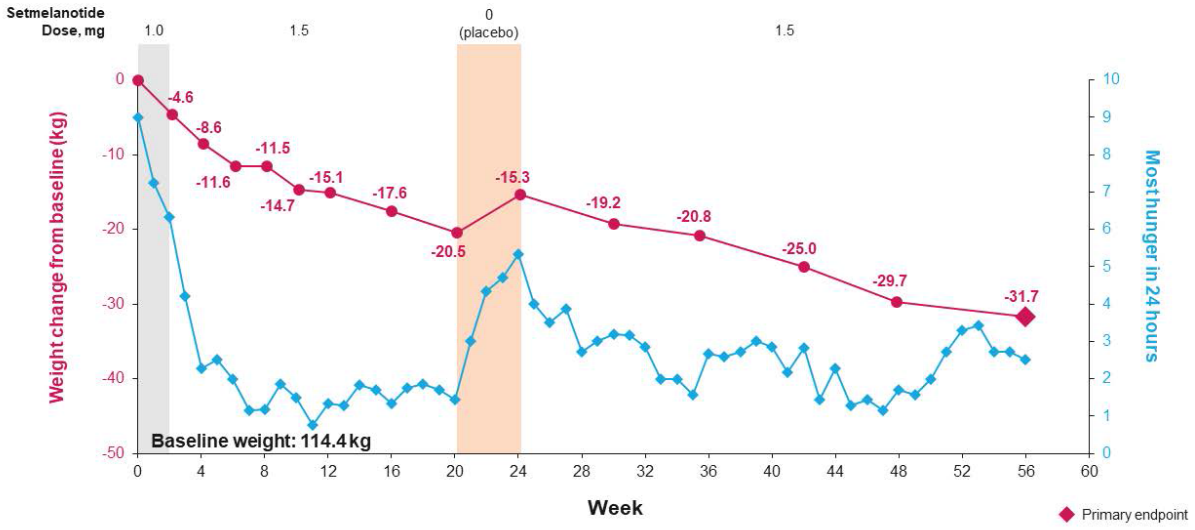
Key Secondary Endpoints:

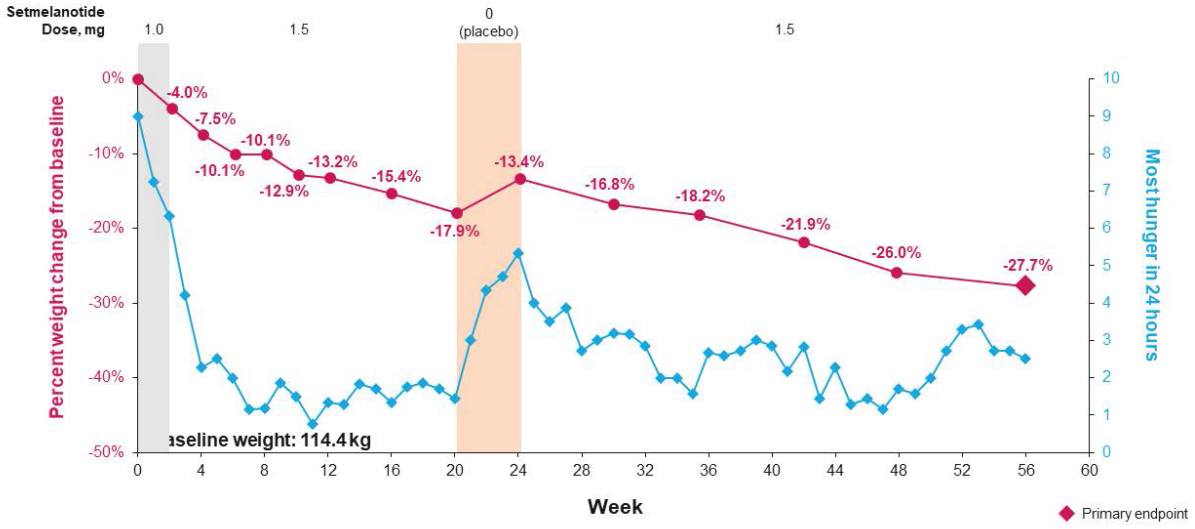
- Percent change in body weight from baseline: -27.7%
- Percent change in hunger score from baseline: -68.8%
- Met ≥25% decrease in hunger score from baseline

Total Treatment

After approximately 52 weeks of treatment at a therapeutic dose of setmelanotide, the patient's body weight decreased 27.1kg (from 105.8 to 82.7 kg).
After approximately 56 weeks of overall treatment with setmelanotide, this patient achieved a total body weight loss of 31.7 kg (from 114.4 to 82.7 kg) and a decrease of hunger scores from 8 at to 2.5.

Figure 8 (b) (6): Weight Change and Weekly Average Hunger Score





Source: Applicant's CSR pg 206/272

Double-Blind, Placebo-controlled Withdrawal Sequence

During the initial 18-week administration of setmelanotide at the 1.5 mg daily dose level, this patient experienced a weight loss of 15.9 kg. Hunger scores ranged between 1 and 2 during the first open-label treatment period indicating a sustained decrease of hunger. The subsequent 4 weeks of placebo resulted in a weight gain of +5.2 kg and hunger scores increase from 1 to 6.

Safety Results

The most common TEAEs reported by the patient were injection site reactions (ISRs); seven (7) of 25 TEAEs reported (28%) were ISRs, all considered probably related to study drug, mild in intensity, and typically lasting 1 day or less. Other TEAEs considered possibly related to study drug by the Investigator included the following: recurrent diarrhea, recurrent headache, tiredness and nausea.
There were no SAEs reported for this patient during treatment with setmelanotide.

Discussion / Conclusions

Overall, treatment with setmelanotide in this patient was well tolerated and led to reduction in hunger and substantial weight loss throughout the study. While the weight loss is likely due to setmelanotide administration, the subject's uncontrolled Type I diabetes may have also played an important factor in the observed results.

Subject (b) (6):

This is a 30-year-old female from France diagnosed with POMC deficiency at 17 years old. Active medical conditions included hypoalbuminemia, orthosis user, anxiety, and abdominal pain. Other medical history included abdominal evisceration (prothesis rejection), sleep apnea syndrome, pulmonary embolism, wound evisceration, and uterine leiomyoma.
Prior intervention for weight loss included gastric balloon (b) (6), deemed ineffective), gastric sleeve (b) (6) 10 kg weight loss which was regained), gastric bypass (b) (6) 50 kg weight loss which was regained), and duodenal switch (b) (6) 100 kg weight loss) per Applicant's CSR.

At the time of study enrollment, the patient was receiving treatment with levokit Ca, pantoprazole, ferrous sulfate, mianserine hydrochloride for anxiety, trineurin and etonogestrel. In addition, the patient received oxycontin to treat sciatica, paracetamol to treat hyperthermia, and fosfomycin trometamol to treat leucocyturia as needed during the study.

Summary Clinical and Laboratory Data:

Parameter	Screening (or first recorded)	End of study
Weight (kg)	152.7	150.5
BMI (kg/m2)	53.31	52.69
HR (bpm)	67.3	68.3
Blood pressure mmHg	102.3/55.7	111/57.5

Waist Circumference (cm)	148	146
Weekly Hunger Scores (max 24h)	7.5	N/A (last recorded on drug 5.7)
Fasting Glucose (mmol/L)	3.9	4
HBA1c (%)	4.2	5.1
Total Cholesterol (mmol/L)	2.46	2.84
HDL	0.88	1
LDL	1.25	1.43
Triglycerides	0.73	0.91

Screening laboratory testing revealed decreased albumin (32 g/L, nl 35-52g/L) considered clinically significant. Otherwise, laboratory measurements were within normal limits, or abnormal without clinical significance.

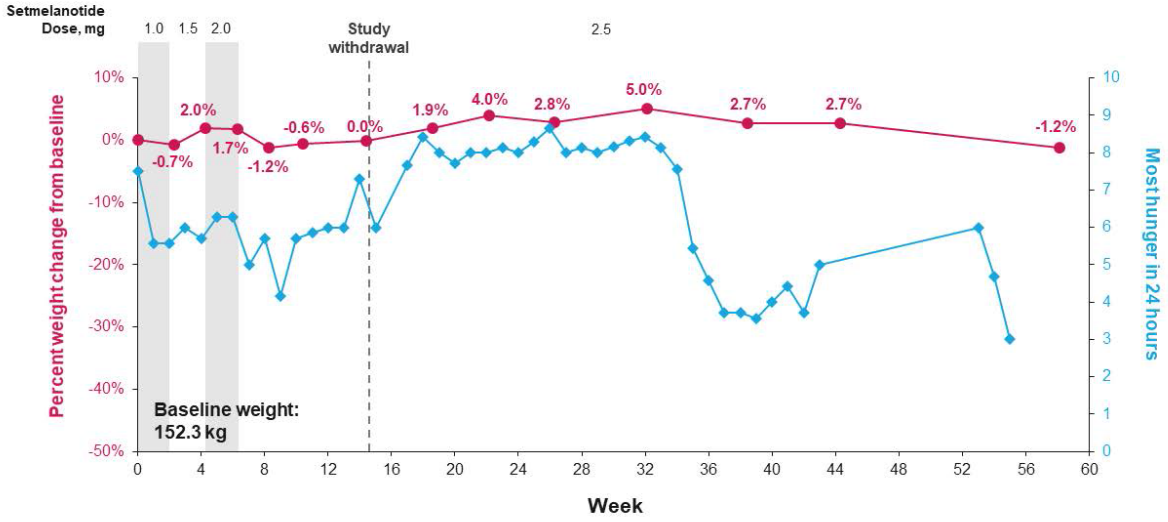
Efficacy Results

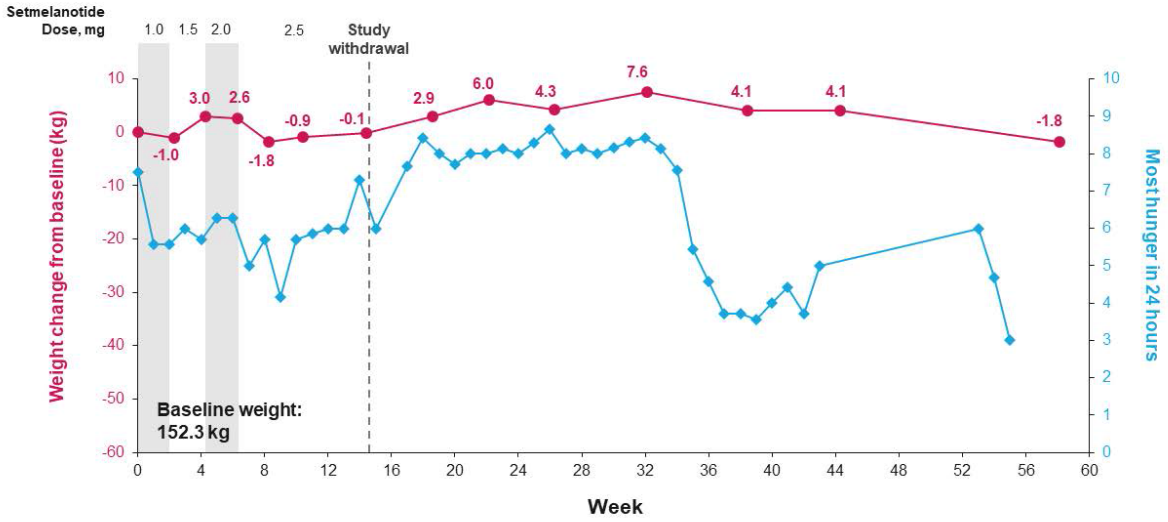
This patient was a non-responder; treatment with setmelanotide was discontinued after the initial open-label treatment period, and additional data were collected while this patient was off drug.

Total Treatment

The patient was administered setmelanotide 2.5 mg daily, during the last 2 weeks of the titration period, and proceeded into the first active treatment period receiving 2.5 mg daily over the next 6 weeks. During the 8-week administration of setmelanotide at the 2.5 mg daily dose level, the patient experienced a weight loss of 2.7 kg. Hunger scores were essentially stable during this treatment period but decreased below 4 (approximately 50% decrease from baseline) during the off-treatment period (weeks 37-42).

Figure 9 (b) (6): Weight Change and Weekly Average Hunger Score





Safety Results

The most common TEAEs reported by the patient were injection site reactions (ISRs); five (5) of 12 TEAEs reported (41.7%) were ISRs, all considered related to study drug, all were mild except 1 which was moderate in intensity, and all typically lasted 1 day or less. Other TEAEs considered possibly related to study drug by the Investigator included hyperpigmentation of skin and fatigue,

both moderate in intensity and considered related to study drug. Hyperpigmentation of skin (duration of 196 days) resolved after setmelantoide treatment was discontinued after patient was determined to be a non-responder. A TEAE of fatigue was considered ongoing. Of note, after discontinuation of treatment, melanin measurements decreased over time, and returned essentially to near pre-study levels.

The subject had an episode of depressive syndrome, mild in intensity which happened off drug (approximately 5 weeks after last dose of study drug). Of note, there was evidence of suicidal ideation at screening.

There were no SAEs reported for this patient during the study.

Discussion / Conclusions

Overall, treatment with setmelanotide in this patient was generally well tolerated, however no weight loss or hunger control was achieved. Of note, the confirmatory genetic testing demonstrated this patient had a benign genetic variant (POMC / c.158A>G, pAsp53Gly_HOM). It is unclear why this patient was not excluded from the study population as a protocol violation.

Subject (b) (6):

This is a 11-year-old female of Arabic descent from Canada. (b) (6) was diagnosed with severe obesity and ACTH deficiency early in infancy. (b) (6) was diagnosed with POMC deficiency at approximately 10 years of age.

Ongoing medical diagnoses at the time of enrollment included gross motor delay, central adrenal insufficiency, type 1 diabetes, microcytic anemia and nightmares.

Concomitant medications were receiving humalog, lantus and novorapid and hydrocortisone. The patient also received advil to treat headaches and betamethasone to treatitchiness, redness and swelling of the skin, both prior to study start. In addition, the patient received zofran for nausea, benadryl and advil for site reactions and itching and redness at the injection site and amoxicillin for strep throat, as needed during the study.

Laboratory parameters measured at baseline were within normal limits or considered not clinically significant.

Summary Clinical and Laboratory Data:

Parameter	Screening (or first recorded)	End of study
Weight (kg)	71.77	57.37
BMI (kg/m2)/BMIz	28.3/2.64	21.31/0.92
HR (bpm)	76	80.3
Blood pressure mmHg	102.7/65	101.3/66.3
Waist Circumference (cm)	104	81
Weekly Hunger Scores (max 24h)	3	2
Fasting Glucose (mmol/L)	13	7.9

HBA1c (%)	7.8	7.8
Total Cholesterol (mmol/L)	3.77	3.43
HDL	1.41	2.02
LDL	2	1.2
Triglycerides	0.74	0.55

Efficacy Results

Primary Endpoint: Met ≥10% Weight Loss

Key Secondary Endpoints:

- Percent change in body weight from baseline: -20.1%
- Percent change in hunger score from baseline: not applicable
- ≥25% decrease in hunger score from baseline: not applicable

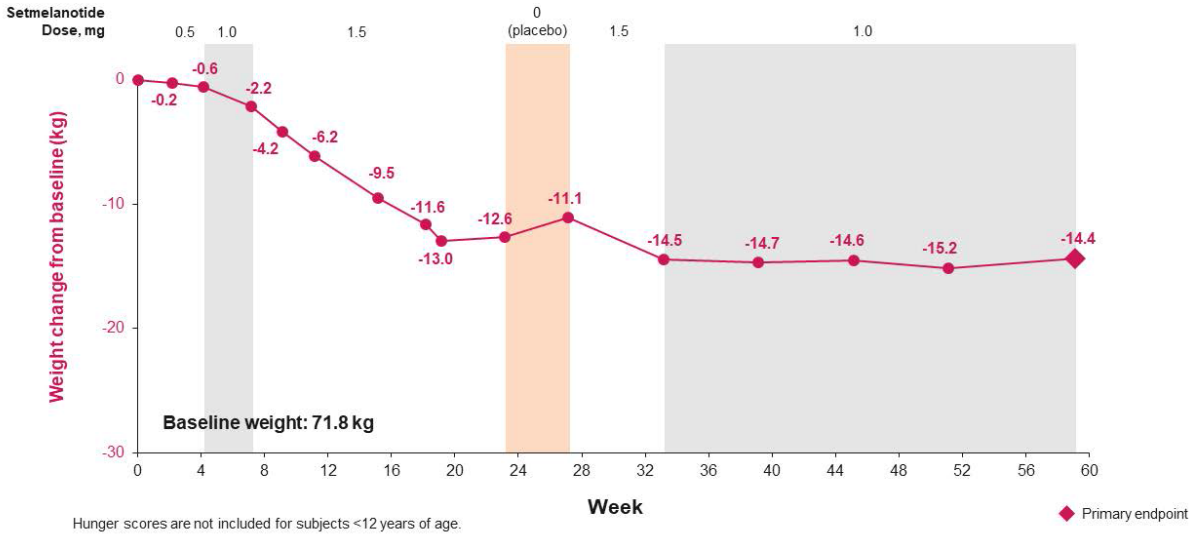
Note: a pediatric hunger scale was utilized given the age of this individual and thus the key secondary endpoints related to hunger were not evaluated as in adults.
The subject's PRO - Hunger Score (weekly average) decreased from 3 to 2 from baseline to end of study. The Global Hunger (question #1 was how hunger was rated now and question #2 was comparing hunger now to the hunger prior to study start) was reported as "moderate hunger" for question 1 and "much less hungry" for question 2.

Total Treatment

After approximately 51 weeks of treatment at the therapeutic dose of setmelanotide, the patient's weight decreased from 69.6 to 57.4 kg and pediatric hunger score remained at ~2 throughout.

After approximately 58 weeks of overall treatment with setmelanotide at the relative therapeutic dose level (1.5 mg or 1.0 mg), this patient achieved a total body weight loss of 14.4 kg (from 71.77 to 57.37 kg).

Figure 10 (b) (6): Weight Change



Source: Applicant's CSR pg 231/272

Double-Blind, Placebo-controlled Withdrawal Sequence

During the 12-week administration of setmelanotide at the 1.5 mg daily dose level, the patient experienced a weight loss of 10.8 kg (0.9 kg per week). Following placebo administration for 4 weeks, the patient gained 1.54 kg of weight.

Safety Results

The most common TEAEs reported by the patient were injection site reactions (ISRs); six (6) of 26 TEAEs reported (23.1%) were ISRs, all considered probably related to study drug, mild to moderate in intensity, and lasting between 1 to 176 days. Other TEAEs considered possibly related to study drug by the Investigator included the following: nausea and hyperpigmentation of the skin. Other events of special interest included, new mole on the skin (face and arm) (reported Day 22, considered moderate in intensity and ongoing) and mild low mood (reported Day 1, lasting 64 days) There were no SAEs reported for this patient.

Discussion / Conclusions

Overall, treatment with setmelanotide in this patient with POMC deficiency obesity was generally well tolerated and led to a substantial, sustained weight loss.
Of note, the patient underwent puberty during the study, evolving from Tanner I at baseline to Tanner IV at the end of study, and gaining 5cm in height. The bone age assessment at screening was advances (13 years, 6 months) which is common in obese children and increased by 1 year during the study, matching the chronological pace, which may in fact represent a slowing down of bone age progression.

Subject (b) (6):

This is a (b) (6). (b) (6) was diagnosed with carnitine deficiency, metabolic acidosis, and short bowel syndrome in early infancy. (b) (6) was diagnosed with a PCSK1 mutation at approximately 1 year of age.
Ongoing medical diagnoses at the time of enrollment included ADHD, asthma, behavioral episodes, easy bruising, contact dermatitis, cough, diabetes insipidus, diarrhea, enuresis, flatulence, history of adrenal insufficiency, history of cardiac arrest, congestive heart failure, metabolic acidosis and seizures, childhood hypertension, imbalance of nutrient intake, insomnia, lactose intolerance, malabsorption syndrome, nocturnal muscle cramps, seasonal allergies, thrombosis, vesicoureteral reflux, vitamin D, pectus excavatum, intermittent fevers and coccidioidomycosis .

At the time of study enrollment, the patient was receiving albuterol sulfate inhaler, fluticasone and montelukast to treat asthma, cetirizine to treat seasonal allergies, cholecalciferol to treat vitamin d deficiency, desmopressin to treat nocturnal enuresis, hydrocortisone to treat contact dermatitis, hydrocortisone pf to treat adrenal crisis, ibuprofen to treat fevers, loperamide to treat diarrhea, melatonin as a sleep aid, multi vitamins/minerals to treat an imbalance of nutrient intake, potassium chloride to treat nocturnal muscle cramps, pseudoephedrine HCL to treat a cough, simethicone to treat flatulence, sodium bicarbonate to treat a pH imbalance, warfarin to treat thrombosis and clonidine to treat hypertension. These medications were administered during the study while being treated with setmelanotide.

In addition, the patient received acetaminophen for fevers, fluconazole for coccidioidomycosis, ferrous sulfate for iron deficiency anemia, Zoloft® and Risperdal® for major depressive disorder, vitamin b12 as a supplemental vitamin and warfarin for thrombosis while being treated with setmelanotide during the study.

Summary Clinical and Laboratory Data:

Parameter	Screening (or first recorded)	End of study
Weight (kg)	55.87	54.52
BMI (kg/m2)/BMIz	26.57/2.66	24.69/2.09
HR (bpm)	68	75.3
Blood pressure mmHg	106.3/69.3	108.7/66
Waist Circumference (cm)	86	84.5
Weekly Hunger Scores (max 24h)	1.33	1.38
Fasting Glucose (mmol/L)	4.27	4.44
HBA1c (%)	5.7	5.2
Total Cholesterol (mmol/L)	2.25	2.66
HDL	0.52	0.93
LDL	1.22	1.33
Triglycerides	1.12	0.88

Efficacy Results

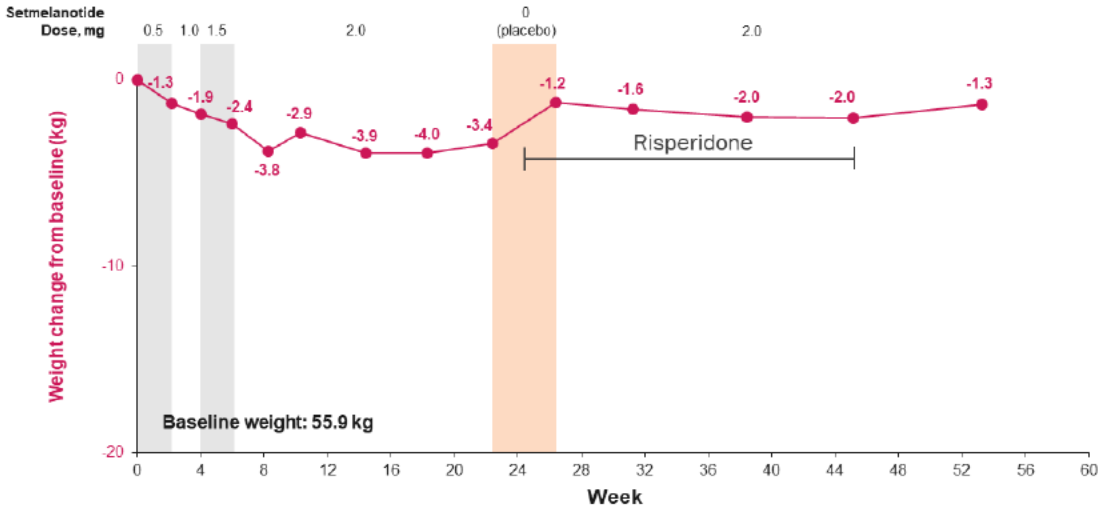
The patient did not meet the primary or key secondary endpoints for the study.

Total Treatment

After approximately 47 weeks of treatment at a therapeutic dose of setmelanotide, the patient's body weight increased from 53.5 to 54.52 kg and pediatric hunger score remained essentially unchanged (from 1.4 to 1.38).

After approximately 53 weeks overall treatment with setmelanotide, this patient experienced a minimal change in body weight (from 55.87 to 54.52 kg) (BMI-Z 2.66 to 2.09) accompanied by a gain in height of 3 cm.

Figure 11. (b) (6): Weight Change



*Subject did not meet primary endpoint. Hunger scores are not included for subjects <12 years of age.

Double-Blind, Placebo-controlled Withdrawal Sequence

During the initial 12-week administration of setmelanotide at the 2.0 mg daily dose level, the patient experienced a weight loss of 1.6 kg. During the subsequent 4 weeks of placebo administration, the patient gained 2.19 kg.

Safety Results

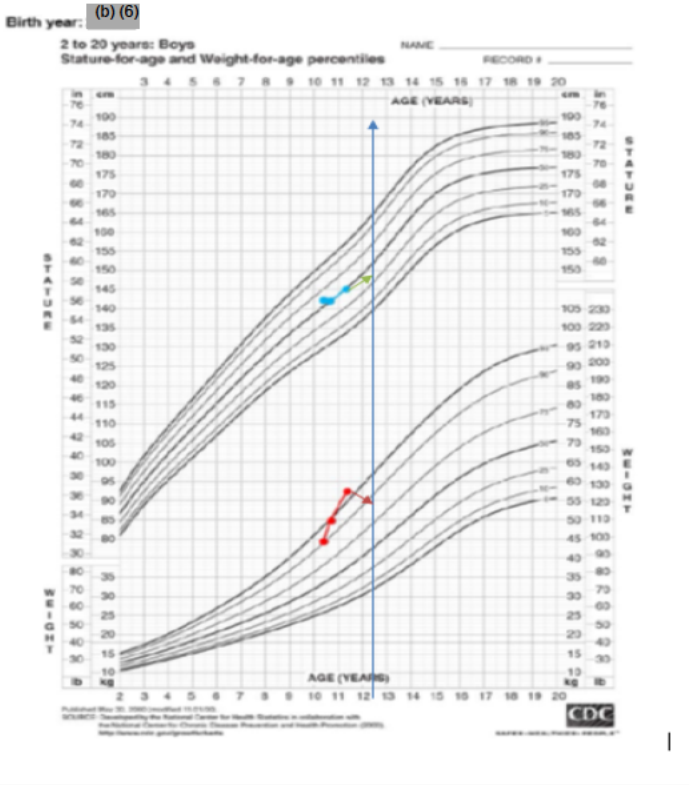
The most common TEAEs reported by the patient were injection site reactions (ISRs); seven (7) of 17 TEAEs reported (41.2%) were ISRs, all considered probably or possibly related to study drug, mild in intensity, and typically lasting 1 to 4 days. The only other TEAE considered possibly related to study drug by the Investigator was hyperpigmentation (legs and trunk).

This patient had 2 SAEs during the study. (b) (6) experienced an SAE of pleuritis during the titration period while being administered 2.0 mg daily. This SAE required hospitalization, was rated severe in intensity, resolved after 2 days and was considered unlikely related to study drug by the Investigator. The second SAE was a major depressive disorder without psychosis episode. The patient also reported suicidal ideation at this time. This SAE was rated severe in intensity, reported Day 162 lasting 7 days, and resulting in hospitalization requiring treatment with Zoloft and Risperdal.

Discussion / Conclusions

Long term treatment with setmelanotide resulted in minimal change in body weight for this subject, from 55.87 to 54.52 kg (BMI-Z 2.66 to 2.09). Additionally, the hunger score difference was negligible throughout the study.
This patient's pubertal development was assessed at Tanner Stage I during screening and at subsequent assessments performed throughout the study. (b) (6) height increased 3.6 cm during the course of the study. At the chronological age of 11 years 6 months, the bone age was read as 13 years. Additionally, the bone age progressed by 6 months in a 1-year period. Below see the subject's plotted weight and height with the historical datapoints available.

Figure 20. Subject (b) (6) height progression.



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Although the subject did not meet the primary or key secondary endpoints for the study, there seems to have been a slowing of weight progression during treatment with setmelanotide as well as a slowing of bone age maturation. The primary endpoint relied on absolute weight values, however in pediatric subjects who continue to grow, a BMI based metric may be better in order to assess clinical benefit. This subject had a reduction in BMIz of 0.57 from 2.66 to 2.09 which is generally considered clinically relevant. Furthermore, this reduction in BMIz was observed during concomitant administration of Risperidone, which has been associated with weight gain. While it is difficult to incorporate the data from this patient in the primary endpoint interpretation, it is reassuring that some degree of response is observed in this subject that is the only PCSK1 patient in the cohort.

Data Quality and Integrity – Reviewers' Assessment

The study was monitored by Rhythm or its designee (both (b) (4) provided monitoring for portions of the study). Monitoring included on-site review of source documents/CRFs for completeness and clarity, cross-checking with source documents. Clarification of administrative matters was also performed. The review of medical records was performed in a manner to ensure that patient confidentiality was maintained.

The site monitor ensured that the investigation was conducted according to protocol design and regulatory requirements by frequent communications (letter, telephone, and fax). Regulatory authorities, the IEC/IRB, and/or Rhythm's clinical quality assurance group or designee may have requested access to all source documents, CRFs, and other study documentation for on-site audit or inspection. Direct access to these documents was guaranteed by the Investigator; the Investigator provided support of these activities throughout the duration of the study.

6.2. RM-493-015

6.2.1. Study Design

Overview and Objective

Title of Study: An Open-label, 1-Year Trial, Including a Double-Blind Placebo-Controlled Withdrawal Period, of Setmelanotide (RM-493), a Melanocortin 4 Receptor (MC4R) Agonist, in Leptin Receptor (LEPR) Deficiency Obesity due to Bi-Allelic Loss-of-Function LEPR Genetic Mutation

Design

Study 015 was a multicenter, open-label, Phase 3 pivotal study to assess long-term (1 year) safety and efficacy of setmelanotide in patients with in leptin receptor (LEPR) deficiency obesity due to bi-allelic loss-of-function LEPR genetic mutation.

The design of this study is identical to that of Study 012 described in the previous section.

The study contains two cohorts of patients: a pivotal cohort and a supplemental cohort.

The study began with an initial period (dose titration) lasting 2 to 12 weeks (dependent upon number of dose escalations required to determine an individual's therapeutic dose). During the dose titration, increments of 0.5 mg dose increases were done at weekly intervals to determine an individual's therapeutic dose, up to the approved maximum dose in the specific country of the participating site (See Table. 1). Thereafter, patients continued active treatment at their specific optimal therapeutic dose for an additional 10 weeks, for a total combined dosing duration of 12 weeks at the individual patient's therapeutic dose.

For a detailed study schema see Figure 3.

Dose selection:

The dose schedule is the same as for Study 012. The Schedule of Assessments (SOA) for study screening and dose titration, the 10-week active treatment and 8-week double-blind placebo withdrawal, and the additional 32-week open-label treatment are depicted in Appendix Table 1.

Objectives:

Primary Objective: To demonstrate statistically significant and clinically meaningful effects of setmelanotide on percent body weight change in patients with leptin receptor (LEPR) deficiency obesity due to rare bi-allelic or loss-of-function mutations at the end of 1 year of treatment.

Secondary objectives: of the study were to assess the effect of treatment with setmelanotide treatment, over 1 year, on the following:

- Safety and tolerability of setmelanotide
- Hunger for patients ≥12 years of age.
- Percent change in body fat mass.
- Glucose parameters
- Waist circumference.
- During withdrawal from drug - reversal of weight and hunger reduction during the double-blind placebo-controlled withdrawal period.

Tertiary objectives: of the study were to assess the effect of setmelanotide treatment over 1 year on the following:

- Percent change in total body mass, non-bone lean mass, and bone density.
- Fasting lipid (cholesterol and triglyceride) panel.
- Pharmacokinetics of setmelanotide.
- C-reactive protein.
- Dose response of setmelanotide through titration procedures.
- Changes in quality of life and health status.

Exploratory objectives: were to assess the effect of setmelanotide treatment over 1 year on the following.

- Hunger in patients ages 6 – 11 years old.
- Changes in neurocognition in patients aged 6 - 16 years old.
- Change in pubertal development
- Change in growth and development
- Ambulatory blood pressure measurement (ABPM), skin pigmentation measured by spectrophotometer, energy expenditure, and 24-hour pharmacokinetic profile
- Hormonal, neuroendocrine, metabolic and anti-inflammatory analytes and biomarker assays.
- If identified, a pharmacokinetic/pharmacodynamics (PK/PD) response employing a suitable endocrine biomarker predictive of setmelanotide target engagement, agonism and efficacy through activation of the MC4R.
- If feasible, correlations of bi-allelic or loss-of-function LEPR genetic mutations and LEPR deficiency due to diverse allelic variants with the magnitude of setmelanotide efficacy endpoints.

Study Endpoints

Primary endpoint: the proportion of patients in the pivotal cohort in the FAS population who met the ≥10% weight loss threshold (responders) after approximately 1 year of treatment.

Key secondary endpoints:

- proportion of patients ≥12 years of age achieving at least 25% improvement in hunger scores following 1 year of treatment with setmelanotide.
- mean percent change in body weight from baseline in the DUS population
- proportion of patients who met responder threshold of ≥25% improvement from baseline in hunger threshold (responders) in the FAS population

For a list of additional secondary, tertiary and exploratory endpoints please see Appendix.

Study Population:

Inclusion Criteria:

1) Bi-allelic, homozygous or compound heterozygous genetic status for the LEPR gene, with the loss-of-function (LOF) variant for each allele conferring a severe obesity phenotype.
2) Age 6 years of age and above.

3) If adult age ≥18 years, obesity with body mass index (BMI) ≥30 kg/m2; if child or adolescent, obesity with BMI ≥95th percentile for age on growth chart assessment.
4) Study participant and/or parent or guardian was able to communicate well with the investigator, to understand and comply with the requirements of the study, and able to understand and sign the written informed consent/assent.
5) Female participants of child-bearing potential must have agreed to use contraception as outlined in the protocol. Female participants of non-childbearing potential did not require contraception during the study.
6) Male participants with female partners of childbearing potential must have agreed to a double barrier method if they became sexually active during the study. Male patients must not have donated sperm during and for 90 days following their participation in the study.

Exclusion Criteria:

1) Recent diet and/or exercise regimen with or without the use of weight loss agents
2) Prior gastric bypass surgery resulting in >10% weight loss durably maintained from the baseline pre-operative weight with no evidence of weight regain.
3) Diagnosis of schizophrenia, bipolar disorder, personality disorder or other Diagnostic and Statistical Manual of Mental Disorders (DSM-III) disorders that the investigator believed would interfere significantly with study compliance.
4) A Patient Health Questionnaire-9 (PHQ-9) score of ≥15.
5) Any suicidal ideation of type 4 or 5 on the Columbia Suicide Severity Rating Scale (C-SSRS). Any lifetime history of a suicide attempt, or any suicidal behavior in the last month.
6) Current, severe stable restrictive or obstructive lung disease
7) History of significant liver disease or liver injury, or current liver assessment for a cause of abnormal liver

Statistical Analysis Plan

The primary endpoint was the proportion of patients in the FAS who demonstrated at least 10% weight reduction at ~1 year (10-14 months post baseline) compared to baseline. The primary research hypothesis was that this proportion is at least 5%. The null hypothesis as that this proportion is at most 5%.

It was expected that treatment with setmelanotide for 1 year would be associated with a TRUE underlying probability of at least 10% weight loss at 1 year of at least 50%. That assumption yielded at least 94% power to yield a statistically significant (alpha=0.05 and 0.025 1-sided, due to discreteness of the binomial distribution) difference from the null hypothesis 5% value for N=10 FAS patients. If the TRUE probability of at least 10% weight loss at 1 year was 40%, then power was ~83%. The minimum OBSERVED proportion of N=10 patients with at least 10% weight loss at 1 year that would have yielded statistical significance (alpha=0.05 and 0.025 1-sided, due to discreteness of the binomial distribution) was 0.3 (3 of 10).

Key Analysis Populations

The following analysis populations were defined:

- The FAS (Full Analysis Set) population was defined as all patients who received any study drug and had at least one baseline assessment (including those who did and did not demonstrate ≥5 kg weight loss or 5% of body weight [if weight was <100 kg at baseline] over 12-week open label treatment period and proceeded into the double blind, placebo-controlled withdrawal period).
- The DUS (Designated Use Set) population was defined as all patients who received any study drug, demonstrated ≥5 kg weight loss or 5% of body weight (if baseline weight was <100 kg) over 12-week open-label treatment period, and proceeded into the double-blind, placebo-controlled withdrawal period.
- The CS (Completers' Set) population was defined as all patients in the DUS population who demonstrated both ≥5 kg weight loss or 5% of body weight (if baseline weight was <100 kg) over 12-week open-label treatment period and continued in the study on active treatment to complete a full year (approximately) of treatment.
- The PP (Per-Protocol) population was defined as the subset of patients in the FAS population with no major protocol violations.
- The SAS (Safety Analysis Set) population was defined as all patients who received any study drug injections at least one post-dose safety assessment.

Handling of Dropouts or Missing Data

The missing data for the primary and key secondary endpoints were handled in the following ways:

- The primary method for handling missing primary/key secondary endpoint data at approximately 1 year first examined the reason for missingness. If unrelated to treatment (e.g., patient moved), the endpoint was either extrapolated using a linear model (y=a+b*study week) based on existing data points or imputed using the longitudinal mixed model for analysis. If the reason for missingness was directly related to treatment (lack of efficacy or an AE), weight change at approximately 1 year was conservatively imputed as 0 kg. Likewise, hunger change at approximately 1 year was imputed as 0. If less than 3 months of data were available for the supplemental patients at the time of first analysis of the combined cohorts, these patients were not imputed and were left out of the analysis until more data were available.
- For categorical endpoints, all patients not ongoing on test treatment and missing their data at 1 year were considered 'failures', for example: for the primary analysis, it was assumed those missing 1-year data did not achieve at least a 10% weight loss from baseline.

Protocol Amendments

The original protocol (30 May 2017) was amended 5 times. The protocol and amendments were revised to accommodate regional regulations of specific individual participating countries, as appropriate. A summary of substantive changes to the protocol is provided in this section and listed in Appendix.

Data Quality and Integrity: Sponsor's Assurance

The study was monitored by Rhythm or its designee (both (b) (4) provided monitoring for portions of the study). Monitoring included on-site review of source documents/CRFs for completeness and clarity, cross-checking with source documents. Clarification of administrative matters was also performed. The review of medical records was performed in a manner to ensure that patient confidentiality was maintained.

The site monitor ensured that the investigation was conducted according to protocol design and regulatory requirements by frequent communications (letter, telephone, and fax). Regulatory authorities, the IEC/IRB, and/or Rhythm's clinical quality assurance group or designee may have requested access to all source documents, CRFs, and other study documentation for on-site audit or inspection. Direct access to these documents was guaranteed by the Investigator; the Investigator provided support of these activities throughout the duration of the study.

6.2.2. Study Results

Compliance with Good Clinical Practices

The study was conducted in accordance with the International Council on Harmonization (ICH) for Good Clinical Practice (GCP) and the appropriate regulatory requirement(s). Essential clinical documents were maintained to demonstrate the validity of the study and the integrity of the data collected. Master files were established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

Financial Disclosure

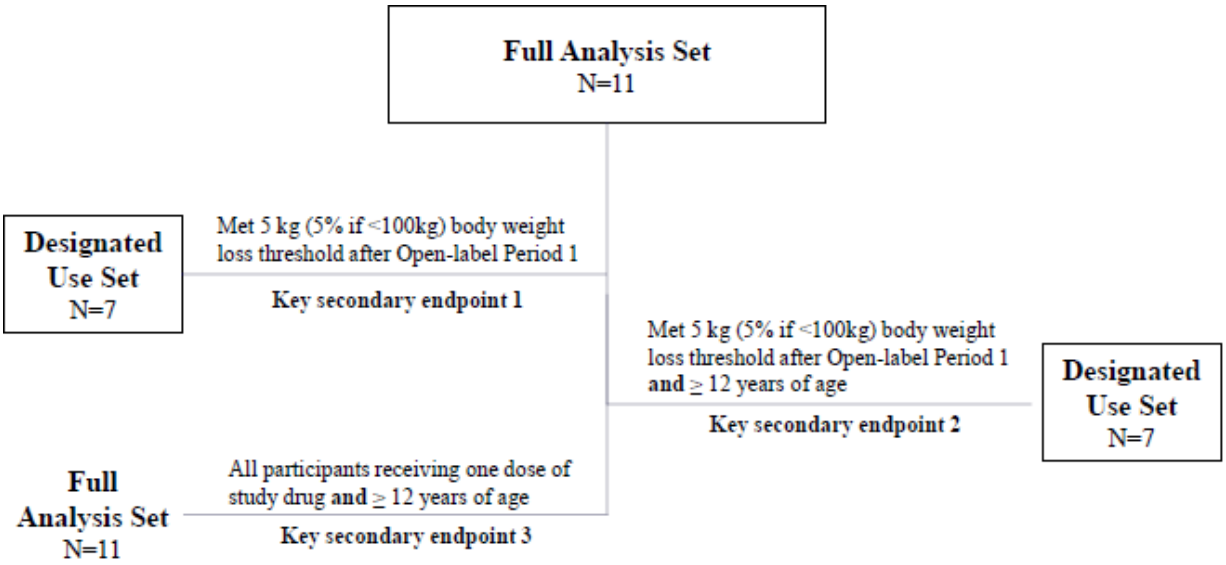
No investigators or sub investigators (study investigators) in Study 012 met the criteria for Financial Interest in the study. Financial Form 3454 was submitted to the NDA.

Patient Disposition

Approximately 10 pivotal patients were scheduled to be enrolled and receive approximately one-year of setmelanotide at daily doses that had been individually titrated for each patient during an initial dose titration (i.e., pivotal patients), with additional supplemental patients who may have received <1 year of treatment at the time of data cutoff (i.e., supplemental patients).

Overall, a total of 11 pivotal patients were enrolled and are the focus of the Study 015 clinical study report (CSR). Additionally, 2 patients were enrolled and received <1 year of treatment and thus were considered supplemental.

Figure 21. Analysis Populations for the Primary and Key Secondary Efficacy Endpoint Analyses



Key secondary endpoint 1: Mean percent change from baseline in body weight (kg) at the end of approximately 1 year of treatment in the DUS.
Key secondary endpoint 2: Mean percent change in weekly average hunger (using "most hunger over the last 24-hours" daily response) from baseline at the end of approximately 1 year of treatment in patients aged 12 years and older in the DUS.

Key secondary endpoint 3: Categorical analysis of the proportion of patients in the FAS who met the ≥25% improvement in hunger threshold (responders) at the end of approximately 1 year of treatment, compared to the proportion from historical data (at most 5% responders in the null population).

Protocol Violations/Deviations

Subject RM493-[redacted] (b) (6) did not meet the criteria of a 5kg weight loss at the end of the 12-week active treatment period but was not discontinued. After discussions with the PI and Medical Monitor, it was decided that the patient will continue treatment at a dose of 2.5 mg (maximum allowable dose in France) pending an opinion from ANSM on increasing the maximum dose to 3.0 mg. The fact that the patient was not discontinued after not meeting the 5kg weight loss threshold and that the active treatment period was extended beyond 12 weeks constitute major protocol deviations.

Table 8. Study RM-493-015 Demographic Characteristics

Parameter	Pivotal Cohort (N=11)	Supplemental Cohort (N=2)	Total (N=13)
Age at Enrollment (years)			
n	11	2	13
Mean (SD)	23.7 (8.39)	18.0 (7.07)	22.8 (8.21)
Median	23.0	18.0	23.0
Q1, Q3	15, 31	13, 23	15, 25
Min, Max	13, 37	13, 23	13, 37
Age Categories, n (%)			
<12 years	0	0	0
≥12 years	11 (100.0)	2 (100.0)	13 (100.0)
Sex, n (%)			
Male	3 (27.3)	2 (100.0)	5 (38.5)
Female	8 (72.7)	0	8 (61.5)
Race, n (%)			
White	10 (90.9)	0	10 (76.9)
Other	1 (9.1)	2 (100.0)	3 (23.1)
South Asian	1 (9.1)	0	1 (7.7)
Unknown	0	2 (100.0)	2 (15.4)
Ethnicity, n (%)			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	11 (100.0)	0	11 (84.6)
Unknown	0	2 (100.0)	2 (15.4)
Country, n (%)			
United Kingdom	1 (9.1)	0	1 (7.7)
United States	0	0	0
France	4 (36.4)	2 (100.0)	6 (46.2)
Germany	3 (27.3)	0	3 (23.1)
Netherlands	3 (27.3)	0	3 (23.1)
Weight (kg)			
n	11	2	13
Mean (SD)	133.265 (26.0200)	158.617 (70.7814)	137.165 (32.7466)
Median	132.300	158.617	132.300
Q1, Q3	115.47, 153.40	108.57, 208.67	115.47, 153.40
Min, Max	89.37, 170.40	108.57, 208.67	89.37, 208.67
Height (cm)			
n	11	2	13
Mean (SD)	166.7 (7.42)	166.5 (9.19)	166.7 (7.27)
Median	166.0	166.5	166.0
Q1, Q3	159, 171	160, 173	160, 171
Min, Max	157, 180	160, 173	157, 180
BMI (kg/m^2)			
n	11	2	13
Mean (SD)	48.17 (10.447)	56.06 (19.312)	49.38 (11.438)
Median	46.63	56.06	46.63
Q1, Q3	38.5, 60.2	42.4, 69.7	40.4, 60.2
Min, Max	35.8, 64.6	42.4, 69.7	35.8, 69.7

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Among all patients with LEPR deficiency obesity in this study, the conditions most commonly reported in the medical history, with most commonly associated with obesity, were vitamin D deficiency and sleep apnea (each 5 patients; 39%); dyslipidemia and hepatic steatosis (each 3 patients; 23%); and arthralgia, delayed puberty, glucose tolerance impaired, hyperuricemia, peripheral venous disease, rhinitis, and type 2 diabetes mellitus (each 2 patients; 15%). All other conditions were reported for one patient only.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Compliance:

Overall treatment duration was 303.1 9(SD 118.03) days in the 11 subjects of the Pivotal Cohort. Five subjects required dose changes/dose interruption with two due to safety concerns and 3 due to efficacy issues.

Per Applicant's CSR all used study drug was collected to assess compliance with the protocol. Patients and/or caretakers were required to maintain a study drug diary to further monitor compliance. The time of dosing was recorded in the patient diary.
If a patient did not receive the entire dose of study drug, the amount administered was to be recorded. In addition, the reason(s) for this partial dose was to be recorded in source documents and the CRF.

The Applicant did not provide a compliance assessment in the CSR; however, the individual compliance diaries were available.

Concomitant medications:

The most common concomitant medications were cholecalciferol (5 of 13 subjects), desloratadine (4 of 13 subjects) and ibuprofen (4 of 13 subjects).

Efficacy Results - Primary Endpoint

The primary endpoint in this study was defined as the proportion of patients in the pivotal cohort in the FAS population who met the ≥10% weight loss threshold (responders) after approximately 1 year of treatment. The primary hypothesis is to compare it to the proportion from historical data (at most 5% responders in the null population). A 90% confidence interval (CI) for the proportion of responders was obtained using the Clopper-Pearson (exact) method. Statistical significance is met if the lower bound of the CI larger than 5%. At least 3 responders out of 10 subjects is needed to achieve statistical significance. In the pivotal cohort, the proportion of patients achieving a ≥10% decrease from baseline in body weight at Week 52 (i.e., after 52 weeks of treatment with setmelanotide at the therapeutic dose) was 45.5% (5/11) (90% confidence interval [CI] 19.96, 72.88; p=0.0001).

The strategy to handle missing data was to impute missing values related to study drug as 0 change from baseline, namely baseline observation carried forward (BOCF), and imputed missing values unrelated to study drug using linear extrapolation, with time as a linear factor in the imputation model in the Applicant's analyses.

The FDA statistical review chose to perform additional sensitivity analyses. The first strategy was to impute all missing data as BOCF, which classifies all subjects with missing values were as non-responders. A second approach, less conservative, was to impute missing values due to adverse event as BOCF and impute missing values unrelated to study drug using multiple imputation (monotone regression).

Per statistical review the visits were grouped as (V3, V4, V5) (V6, V7, V8) (V9, V10, V11, V12). Averages were taken among the visits within each group and were used in the imputation model together with baseline values. The three subjects who did not enter the withdrawal period were not included in imputation. For analyses of the binary endpoints, continuous body weights or hunger scores at 1 year were converted to binary values. Asymptotic standard errors for proportions were used in application of Rubin's rule.

Among the 5 patients who achieved >10% weight loss in 52 weeks (Patient (b) (6), Patient (b) (6), Patient (b) (6), Patient (b) (6), and Patient (b) (6)), a maximum percent decrease from baseline to Week 52 in weight of 25% was seen. Note that Patient (b) (6) died secondary to injuries sustained as a passenger in an automobile accident prior to Week 52; this patient experienced a percent decrease from baseline in weight of -16.7% at (b) (6) last assessment prior to discontinuation (Visit 9; Day 225 [Week 32]).

Of the 6 patients who did not reach the primary endpoint and achieve 10% weight loss in 52 weeks the following weight loss was achieved:

• Patient (b) (6) discontinued setmelanotide due to Grade 1 eosinophilia prior to Week 52; this patient experienced a percent decrease from baseline in weight of -1.4% at the last assessment prior to discontinuation (Visit 3; Day 57 [Week 8]).

• Patient (b) (6) had a maximum percent decrease from baseline in weight of -3.7% on Day 301 (Week 43) and a percent decrease from baseline in weight of -2.5% at the last assessment (Day 364 [Week 52]).

• Patient (b) (6) had a maximum percent decrease from baseline in weight of -5.7% on Day 285 (Week 41) and a percent decrease from baseline in weight of -2.3% at the last assessment (Day 414 [Week 59]). Based on PK data, which showed aberrant setmelanotide concentrations from approximately Visit 5 through Visit 12, it was suspected that this patient was not taking study drug according to the prescribed regimen (see Section 11.2.1 and RM-493-015 PK Report for details).

• Patient (b) (6) had a maximum percent decrease from baseline in weight of -15.3% on Day 176 (Week 25) and a percent decrease from baseline in weight of -9.8% at the last assessment (Day 414 [Week 59]). Based on PK data, which showed aberrant setmelanotide concentrations from approximately Visit 5 through Visit 12, it was suspected that this patient was not taking study drug according to the prescribed regimen (see Section 11.2.1 and RM-493-015 PK Report for details).

• Patient (b) (6) had a maximum percent decrease from baseline in weight of -11.7% on Day 176 (Week 25) and a percent change from baseline in weight of -0.1% at the last assessment (Day 414 [Week 59]). Based on PK data, which showed aberrant setmelanotide concentrations from approximately Visit 5 through Visit 12, it was suspected that this patient was not taking study drug according to the prescribed regimen (see Section 11.2.1 and RM-493-015 PK Report for details).

• Patient (b) (6) had a maximum percent decrease from baseline in weight of -5.9% on Day 200 (~Week 29) and a percent decrease from baseline in weight of -0.9% at the last assessment (Day 445 [~Week 63]).

Key Secondary Endpoints:

A case by case review was performed and is available below:

Subject (b) (4):

This is a (b) (6) with diagnosis of LEPR deficiency obesity since age 10. Ongoing medical conditions at the time of enrollment included defective hearing, microcytic anemia, and vitamin D deficiency. Comorbidities likely related to obesity included dyslipidemia and hyperinsulinemia. At enrollment, this patient was receiving Vitamin D to treat vitamin D deficiency; iron and folic acid to treat microcytic anemia; simethicone for gastrointestinal disorders, and magnesium and other dietary supplements. These medications were administered concomitantly with setmelanotide throughout the study.

Summary Clinical and Laboratory Data:

Parameter	Screening (or first recorded)	End of study
Weight (kg)	118.1	90.75
BMI (kg/m2)	42.9	32.15
HR (bpm)	80.7	62.7
Blood pressure mmHg	115/66.3	117.7/70.7
Waist Circumference (cm)	114	105.5
Weekly Hunger Scores (24h)	6.83	4
Fasting Glucose (mmol/L)	0.59	0.57
HBA1c (%)	5.8	5.5
Total Cholesterol (mmol/L)	3.9	3.1
HDL	0.7	0.9
LDL	2.7	2.1
Triglycerides	2.3	0.8

The patient had mildly decreased hemoglobin (114 g/L; normal range 128 to 168 g/L) and hematocrit (35%; normal range 38 to 49%) at baseline.

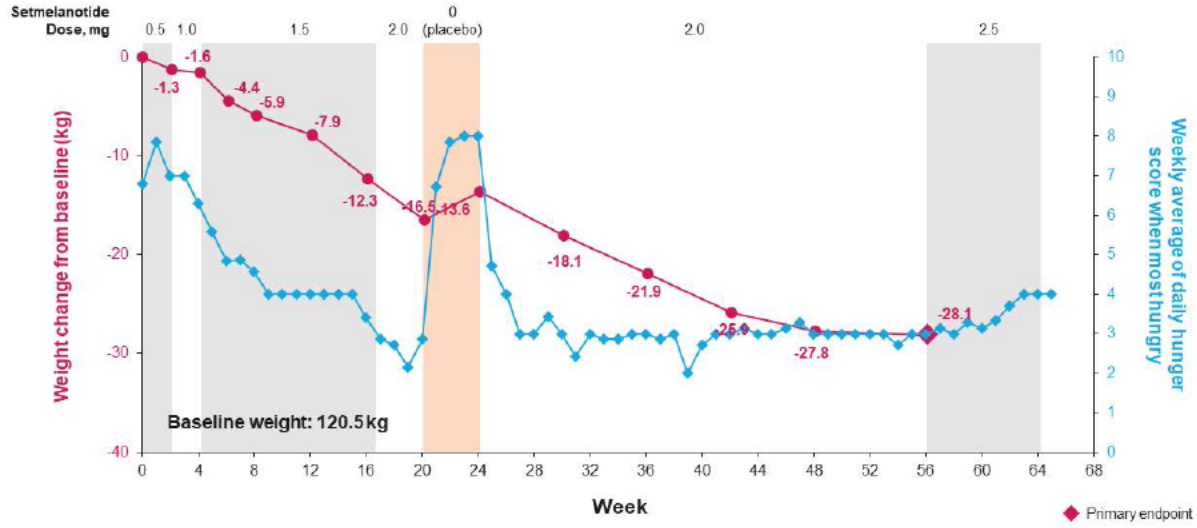
Efficacy Results:

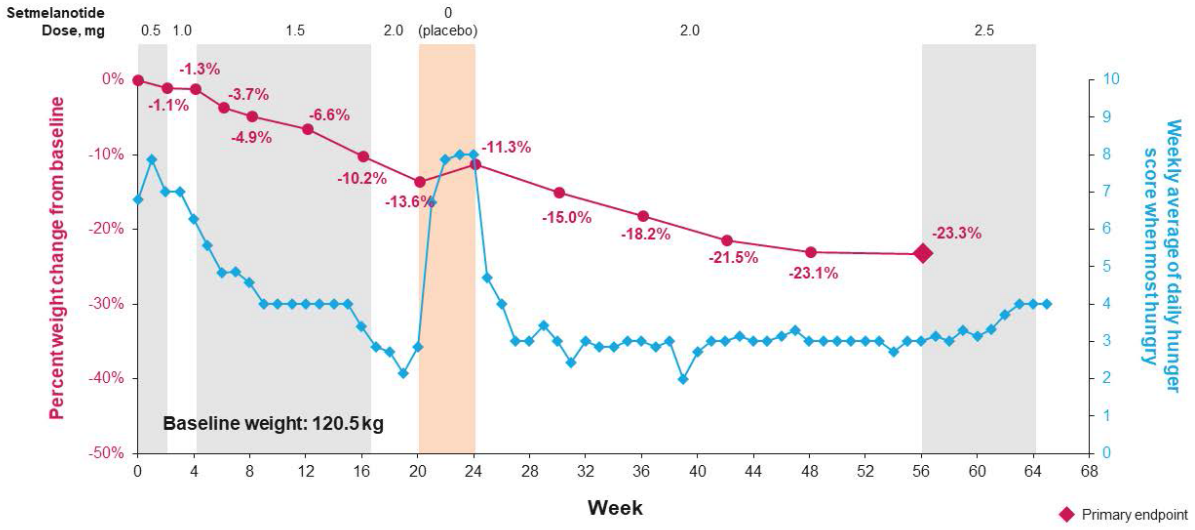
Primary Endpoint: Met ≥10% Weight Loss
Key Secondary Endpoints:
- Percent change in body weight from baseline: -23.3%
- Percent change in hunger score from baseline: -56.08%
- Met ≥25% decrease in hunger score from baseline

Total Treatment

After approximately 48 weeks of treatment, the patient's body weight decreased from 119 kg to 90.8 kg and hunger score improved from 6.3 to 3.0. The patient's waist circumference decreased from 125 to 105.5 cm at the last assessment, and BMI decreased from 43.2 to 32.2 kg/m2.

Figure 22. (b) (6) Weight change and weekly average hunger score





Double-Blind, Placebo-Controlled Withdrawal Sequence

After receiving placebo for 4 weeks, the patient gained 2.9 kg of weight, and (b) (6) hunger scores increased from 2.9 at Week 19 to 8.0 at Week 24.

Safety results:

The most frequent TEAEs reported by the patient were injection site reactions 15 of 26 (57.7%), mild in intensity, and typically lasting between 2 to 8 weeks. The second most common AEs were nausea and abdominal pain.

Of note the subject experienced an episode of perceptual disorder (AEDECOD of illusion). This was considered moderate in intensity, and per investigator's assessment likely not related to drug administration. The event was ongoing at the end of study. No additional data is available about this episode.

This patient did not experience any SAEs.

Discussion / Conclusions

Overall, treatment with setmelanotide in this patient with LEPR deficiency obesity was well tolerated and led to reduction in hunger and substantial weight loss. The AE of perceptual disorder may be relevant in the context of a centrally acting drug; therefore, I consider this AE as likely drug related at this time.

Subject (b) (6):

This is a (b) (6) with LEPR deficiency obesity diagnosed at 29 years of age. (b) (6) past medical history included gastric banding, hypokalemia, sigmoid adenoma, varices of legs, and venous surgery. (b) (6) underwent a gastric banding procedure and lost a total of 44 kg, but subsequently regained the weight. Ongoing condition at baseline included atopic dermatitis and vitamin D deficiency. At enrollment, this patient was receiving centrum A to Zinc and vigantolette to treat zinc deficiency and vitamin D deficiency, respectively. These medications were administered concomitantly with setmelanotide throughout the study.

Summary Clinical and Laboratory Data:

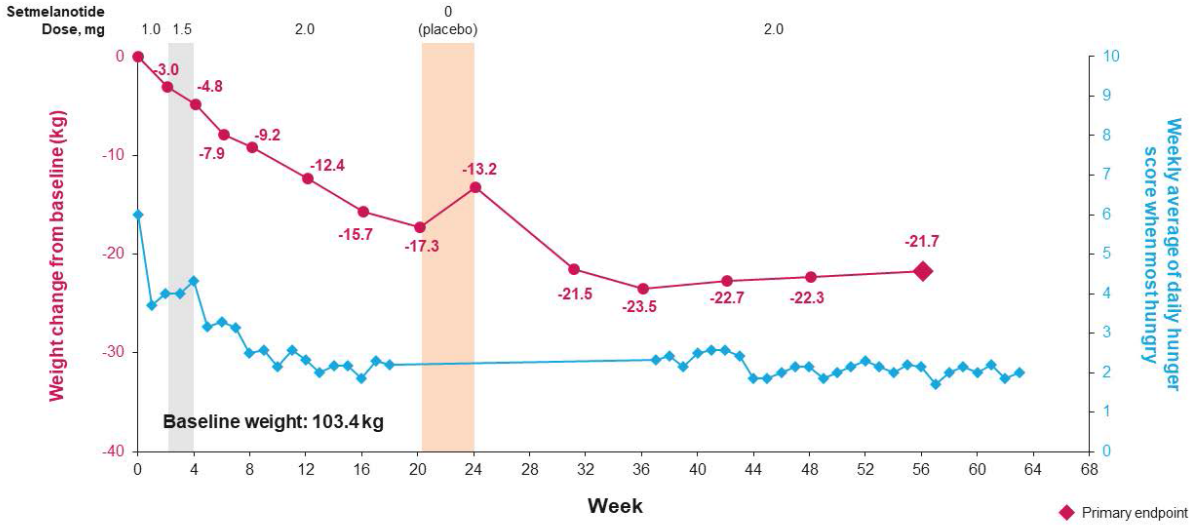
Parameter	Screening (or first recorded)	End of study
Weight (kg)	103.43	83
BMI (kg/m2)	35.79	28.38
HR (bpm)	59	81.3
Blood pressure mmHg	103.7/69	111/77.3
Waist Circumference (cm)	108	98
Weekly Hunger Scores (24h)	6	2.0
Fasting Glucose (mmol/L)	0.56	0.56
HBA1c (%)	5.3	5.4
Total Cholesterol (mmol/L)	3.2	3.4
HDL	1.4	1.5
LDL	1.8	1.9
Triglycerides	1	0.8

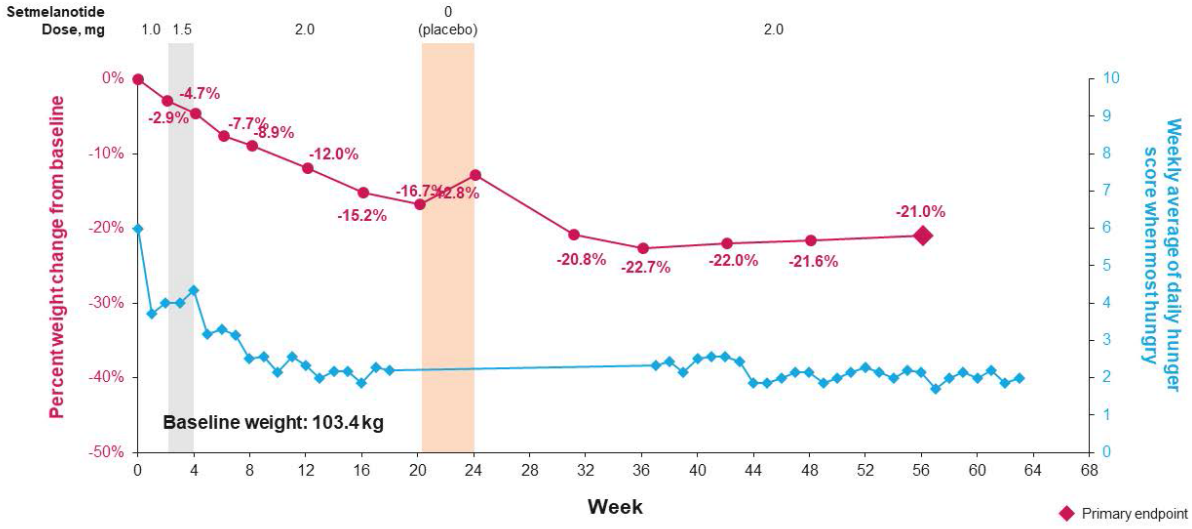
Efficacy Results:
Primary Endpoint: Met ≥10% Weight Loss
Key Secondary Endpoints:
– Percent change in body weight from baseline: -21.0%
– Percent change in hunger score from baseline: -64.3%
– Met ≥25% decrease in hunger score from baseline

Total Treatment:

Over the course of treatment in the study the patient's body weight decreased from 103.4 to 80.7 kg and hunger score improved from 6.0 to 2.0. The patient's waist circumference decreased from 108 to 98 cm at the last assessment, and BMI decreased from 35.8 to 28.4 kg/m_2 over this time period.

Figure 23. (b) (6) Weight change and weekly average hunger score





Double-Blind, Placebo-Controlled Withdrawal Sequence:

After receiving placebo for 4 weeks, the patient's weight increased from 86.1 kg to 90.2 kg. There were no data for hunger scores during these visits.

Safety Results:

Overall, the patient experienced a total of 35 treatment-emergent adverse events, of which 3 were severe (Grade 3) in intensity, headache, leg muscle spasms, and back pain, with headache considered study drug-related. Most AEs were mild to moderate injection site reactions. Other events of special interest experienced by this patient included 5 episodes of nausea, mild in intensity and of short duration. The patient also experienced the sexual events of spontaneous intermittent erections and no ejaculation during intercourse despite erections, with these events assessed as mild to moderate in intensity.
This patient did not experience any SAEs.

Discussion / Conclusions

This patient met the primary and key secondary efficacy endpoints. Although the patient experienced a Grade 3 study drug-related TEAE (headache), most TEAEs reported were typically mild to moderate in intensity and considered resolved during the study. The TEAEs considered related to setmelanotide were generally consistent with those observed in other studies of setmelanotide (i.e., ISRs, sexual events, nausea).

Subject (b) (6)

This is a (b) (6) with LEPR deficiency obesity diagnosed at 11 years of age. The patient had a prior medical history of gastrectomy. This patient had a gastric sleeve procedure in (b) (6) and lost approximately 48 kg (180 kg to ~140 kg) following the surgery. However, (b) (6) regained the weight over approximately 1.5 years. Ongoing conditions included hyperuricemia, iron deficiency, anemia, and vitamin D deficiency. Comorbidities likely related to obesity included impaired glucose tolerance, sleep apnea syndrome, dyslipidemia, steatosis hepatitis, and gastroesophageal reflux.
At enrollment, this patient was receiving ferrous sulfate, colecalciferol and folic acid to treat iron deficiency, omeprazole to treat gastroesophageal reflux. These medications were administered concomitantly with setmelanotide throughout the study. In addition, this patient was administered iron infusion for iron deficiency and vigantolette for vitamin D deficiency as needed during the study.

Summary Clinical and Laboratory Data:

Parameter	Screening (or first recorded)	End of study
Weight (kg)	170.4	143.75
BMI (kg/m2)	61.84	52.8
HR (bpm)	97	90
Blood pressure mmHg	120.3/72.7	97.3/63.3
Waist Circumference (cm)	154	136.5

Weekly Hunger Scores (24h)	7	2.33
Fasting Glucose (mmol/L)	0.54	0.53
HBA1c (%)	5.3	4.7
Total Cholesterol (mmol/L)	4.2	3.8
HDL	1	1
LDL	3.5	2.7
Triglycerides	1.2	1

Efficacy Results:

Primary Endpoint: Met ≥10% Weight Loss

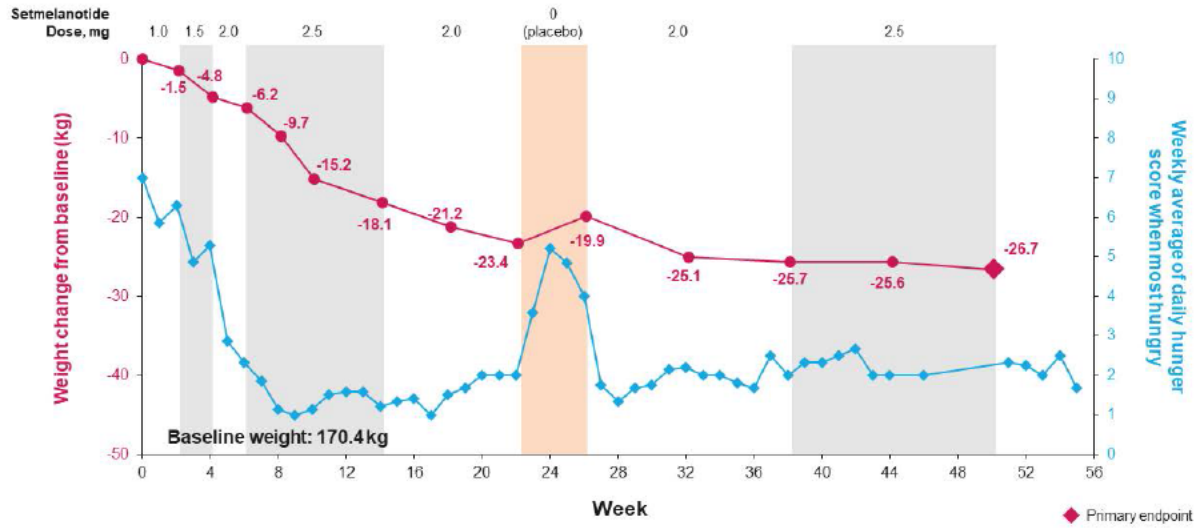
Key Secondary Endpoints:

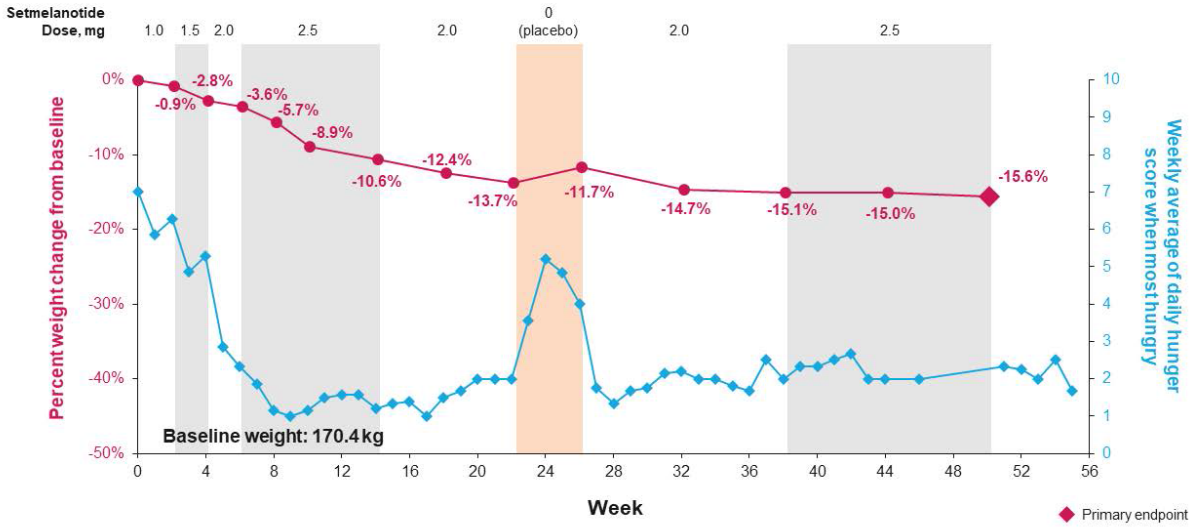
- Percent change in body weight from baseline: -15.6%
- Percent change in hunger score* from baseline: -66.7%
- Met ≥25% decrease in hunger score* from baseline

Total Treatment

Over the course of treatment in the study, the patient's body weight decreased from 170.4 to 143.8 kg and hunger score improved from 7.0 to 2.3. The patient's waist circumference decreased from 154 to 136.5 cm, and BMI decreased from 61.8 to 52.8 kg/m2.

Figure 24. (b) (6) Weight change and weekly average hunger score





Double-Blind, Placebo-Controlled Withdrawal Sequence

After receiving placebo for 4 weeks, the patient's weight increased from 147.0 to 150.5 kg, and hunger scores increased from 2 to 4.

Safety Results:

Overall, treatment-emergent adverse events (TEAEs) were generally considered mild in intensity and resolved during the study. The most common TEAEs reported were injection site reactions (ISRs); 7 of 20 TEAEs reported (35%) were ISRs, all considered probably related to study drug, mild in intensity, and typically lasting between 2 to 8 weeks. The second most common AE reported was headache (3 of 20). Of interest the subject also experienced 2 episodes of syncope and an episode of depressed mood.
This patient did not experience any SAEs.

Discussion / Conclusions

This patient met the primary and key secondary efficacy endpoints. The TEAEs considered related to setmelanotide were generally consistent with those observed in other studies of setmelanotide, ISRs, headache. The subject experienced depressed mood that was moderate in intensity and was considered probably related by the investigator.

Subject (b) (6):

This is a (b) (6) with LEPR deficiency obesity diagnosed at age 27. The patient's prior medical history included ovarian teratoma. Ongoing medical conditions at the time of enrollment included defective hearing, microcytic anemia, and vitamin D deficiency. Comorbidities likely related to obesity included dyslipidemia and hyperinsulinemia.

Ongoing medical history included egg allergy, hypothyroidism, intestinal diverticulum, depression, delayed puberty, and stature delay. Comorbidities likely related to obesity included sleep apnea syndrome.

At enrollment, this patient was receiving Seresta, fluoxetine, and quetiapine to treat depressive syndrome, Diprosone, Inorial, and tridesonit to treat allergies, cholecalciferol to prevent vitamin D deficiency, Imodium to treat diarrhea, Levothyrox to treat hypothyroidism, speciafoldine to prevent folic acid deficiency and tardyferon to prevent iron deficiency. These medications were administered concomitantly with setmelanotide throughout the study. In addition, the patient received Azinc Optimal to prevent zinc deficiencies and Uvedose to prevent vitamin d deficiency during the study.

Summary Clinical and Laboratory Data:

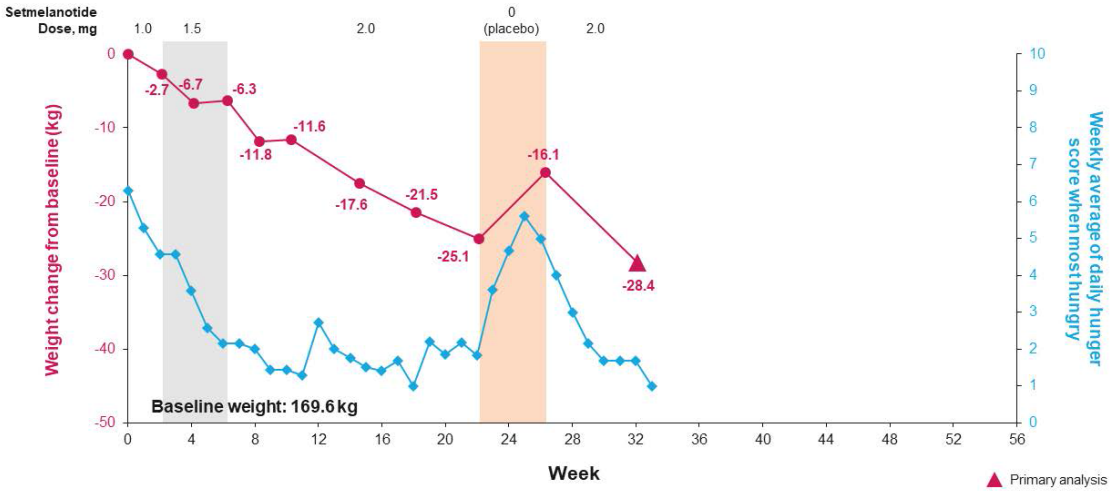
Parameter	Screening (or first recorded)	End of study
Weight (kg)	169.57	141.2
BMI (kg/m2)	64.61	53.8
HR (bpm)	78.3	78
Blood pressure mmHg	134/72	138/71
Waist Circumference (cm)	150	141
Weekly Hunger Scores (24h)	6.29	1
Fasting Glucose (mmol/L)	4.9	5
HBA1c (%)	5.8	5.4
Total Cholesterol (mmol/L)	1.86	4.17
HDL	0.51	1.19
LDL	1.09	2.56
Triglycerides	1.28	0.93

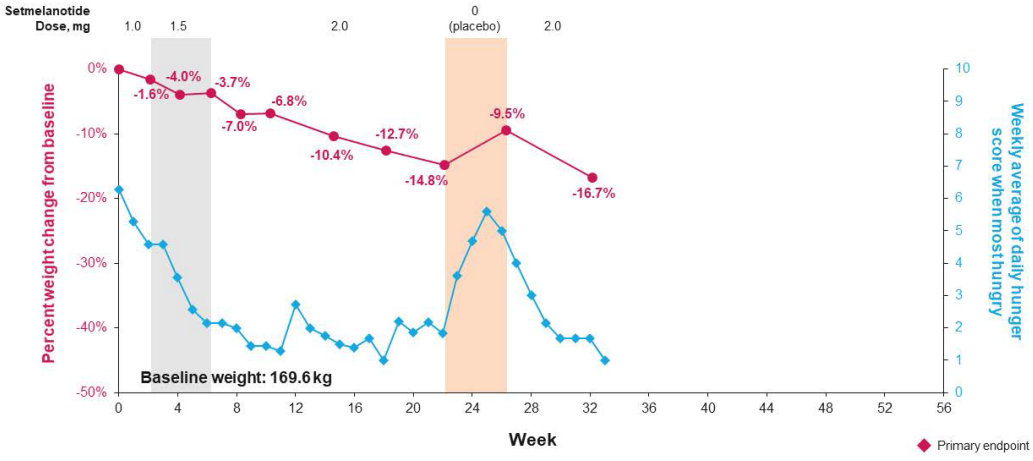
Efficacy Results
Primary Endpoint: Met ≥10% Weight Loss
Key Secondary Endpoints:
– Percent change in body weight from baseline: -16.7%
– Percent change in hunger score from baseline: -52.7%
– Met ≥25% decrease in hunger score from baseline

Total Treatment

Over the course of treatment in the study, the patient's body weight decreased from 169.6 to 141.9 kg and hunger score improved from 6.3 to 1.0. Over this same time period, waist circumference decreased from 150 to 141 cm, and BMI decreased from to 64.6 to 53.8 kg/m2.

Figure 25. (b) (6) Weight change and weekly average hunger score





Double-Blind, Placebo-Controlled Withdrawal Sequence

Following treatment with placebo, the patient's weight increased from 144.5 to 153.5 kg, and (b) (6) hunger score increased from 1.8 to 5.0.

Safety Results

The most common TEAEs reported were asthenia, hypochondrial pain, and injection site reactions (ISRs); 3 of 21 TEAEs reported (14.3%) were ISRs, all considered probably related to study drug, mild in intensity, and typically lasting 29 days or less. Other TEAEs considered possibly related to study drug by the Investigator included the following: fatigue, scar pigmentation and focal skin hyperpigmentation, nausea, renal insufficiency, vertigo, cholestasis, hepatic cytolysis, left hypochondrial pain, xerosis, and asthenia. As stated previously, the patient died due to injuries sustained as a passenger in an automobile accident (an SAE).

Discussion / Conclusions

This patient had experienced substantial weight loss and reduction in hunger scores at the time of premature death at week 26 of the study. If weight loss and reduction in hunger scores had been maintained, the patient would have met the primary and key secondary efficacy endpoints. Except for ongoing TEAEs related to hyperpigmentation and xerosis, TEAEs reported were typically mild in intensity and considered resolved during the study.

Subject (b) (6)

This is a (b) (6) with LEPR deficiency obesity diagnosed at age 27. The patient's prior medical history included kidney stones, right humerus fracture and right clavicle fracture. Prior interventions for obesity include surgery for a gastric ring in (b) (6), with any associated weight loss not reported.

Summary Clinical and Laboratory Data:

Parameter	Screening (or first recorded)	End of study
Weight (kg)	124.8	104
BMI (kg/m2)	38.52	32.1
HR (bpm)	57.3	57.7
Blood pressure mmHg	116.7/77.3	115.3/79
Waist Circumference (cm)	120	108
Weekly Hunger Scores (24h)	8.43	6.71
Fasting Glucose (mmol/L)	4.1	
HBA1c (%)	5.3	4.9
Total Cholesterol (mmol/L)	4.5	3.85
HDL	0.97	1.27

LDL	3.03	2.32
Triglycerides	1.1	0.58

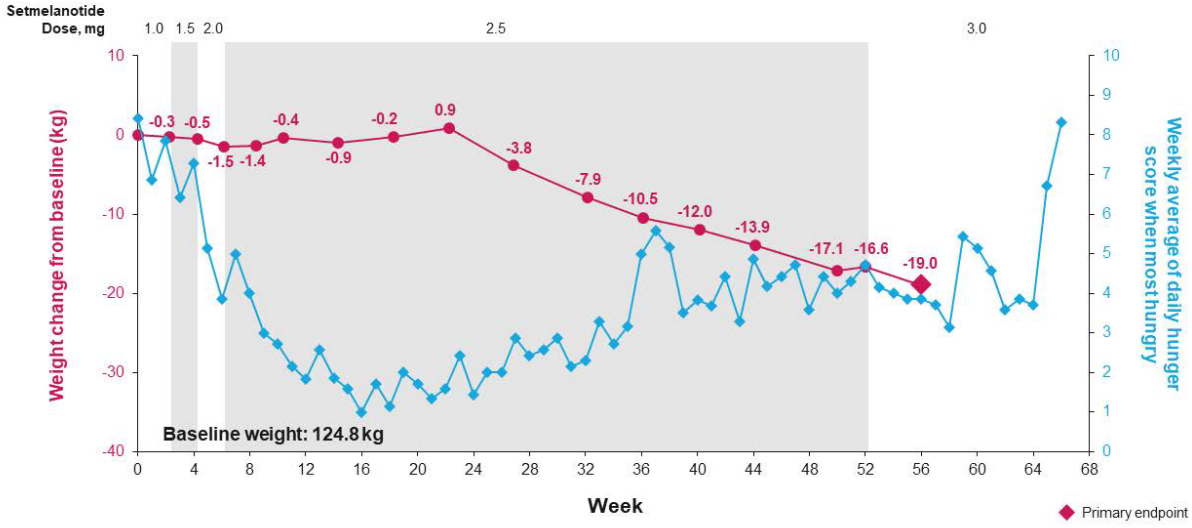
Efficacy Endpoints
Primary Endpoint: Met ≥10% Weight Loss

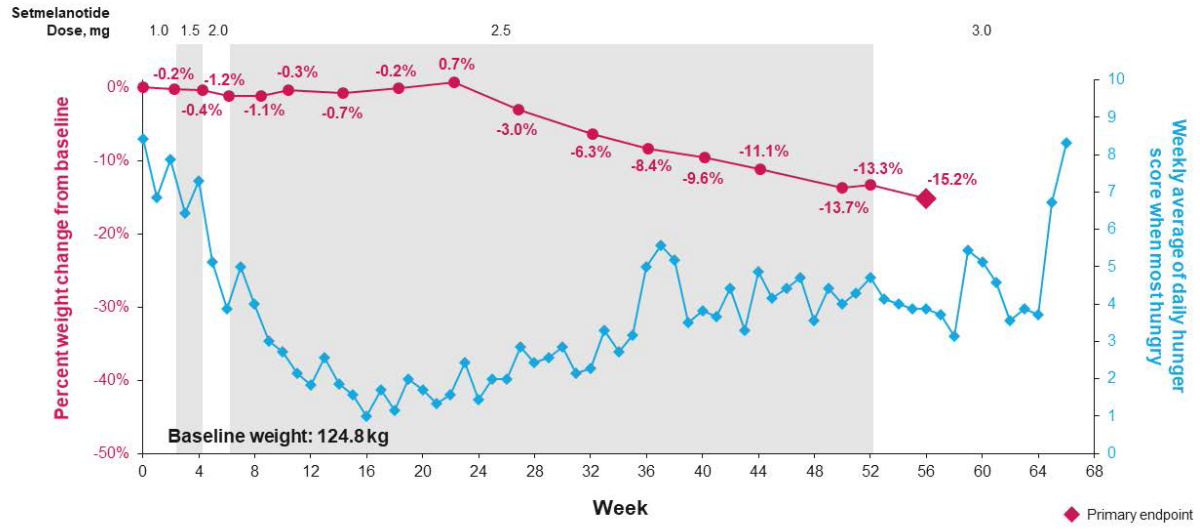
Key Secondary Endpoints:
– Percent change in body weight from baseline: -15.2%
– Percent change in hunger score from baseline: -54.2%
– Met ≥25% decrease in hunger score from baseline

Total Treatment

Over the course of treatment in the study, the patient's body weight decreased from 124.8 to 116.9 kg and hunger score improved from 8.4 to 6.7. Over this same time period, waist circumference decreased from 120 to 108 cm, and BMI decreased from to 38.5 to 32.1 kg/m2.

Figure 26. (b) (6) Weight change and weekly average hunger score





Double-Blind, Placebo-Controlled Withdrawal Sequence

The patient did not participate in the Placebo Withdrawal Period as (b) (6) did not technically reach the therapeutic dose or qualify as a DUS patient. Although the patient initially did not meet the 5 kg threshold during Open-label Treatment Period 1 (at 12 weeks, meaning (b) (6) did not qualify as a DUS patient), (b) (6) showed a reduction in hunger and the Investigator continued to treat the patient at 2.5 mg at unscheduled visits until regulatory approval to increase the dose. The patient was administered setmelanotide 2.5 mg daily (as the therapeutic dose), for a total of 56 weeks. During this period, the patient's weight changed from 123.4 kg to 108.2 kg, and hunger scores increased from 3.29 to 4.29.

Thereafter, after regulatory approval, the patient's dose was increased to 3.0 on (b) (6), after which, (b) (6) weight decreased to over 3 months to 104 kg by (b) (6) final study visit. Since beginning administration of setmelanotide (Day 1 through to the final week of Open-label Period 1), the patient's weight decreased from 124.8 to 104.0 kg, and hunger score decreased from 8.4 to 6.7.

Safety Results

Only 2 TEAEs reported were injection site reactions (ISRs) of 32 TEAEs reported (6%) by this patient. Other TEAEs considered possibly related to study drug by the Investigator included the following: nausea, abdominal pain, diarrhea, depression, asthenia, insomnia, right shoulder and buttock pain, right sciatica, right rib, shoulder, and costal pain, plantar and glans penis nevi, and abdominal lipodystrophy.

The most common treatment-emergent events of special interest experienced by this patient were related to mood disorders (e.g., depression and suicidal ideation), with 1 event of special interest of suicidal ideation considered ongoing at data lock.

Discussion / Conclusions

This patient met the primary and key secondary efficacy endpoints; however, (b) (6) was not part of the DUS as (b) (6) had not achieved 5% weight loss after titration period. The TEAEs were ISRs, nausea, abdominal pain and depression with suicidal ideation.

Subject (b) (6):

This is a (b) (6) with LEPR deficiency obesity diagnosed at age 16. The patient's prior medical history included an ovarian cyst. The patient had an ongoing medical history of vitamin D deficiency. Comorbidities likely related to obesity included fatty liver, venous insufficiency, type 2 diabetes, and sleep apnea syndrome.

At enrollment, this patient was receiving Humalog, Stagid, and Trulicity to treat diabetes. These medications were administered concomitantly with setmelanotide throughout the study. In addition, the patient received ramipril for renal protection and clamoxyl and cefixime to treat a head and neck infection, as needed during the study.

Summary Clinical and Laboratory Data:

Parameter	Screening (or first recorded)	End of study
Weight (kg)	150.3	146.5
BMI (kg/m2)	60.21	58.68
HR (bpm)	97.7	81
Blood pressure mmHg	125.3/70	103.7/51.7
Waist Circumference (cm)	141	139
Weekly Hunger Scores (24h)	8	
Fasting Glucose (mmol/L)		
HBA1c (%)	7.6	6.6
Total Cholesterol (mmol/L)	3.89	3.59
HDL	0.94	0.99
LDL	2.62	2.21
Triglycerides	0.72	0.85

Efficacy Endpoints
Primary Endpoint: Did Not Meet ≥10% Weight Loss

Key Secondary Endpoints: – Percent change in body weight from baseline: -2.5%

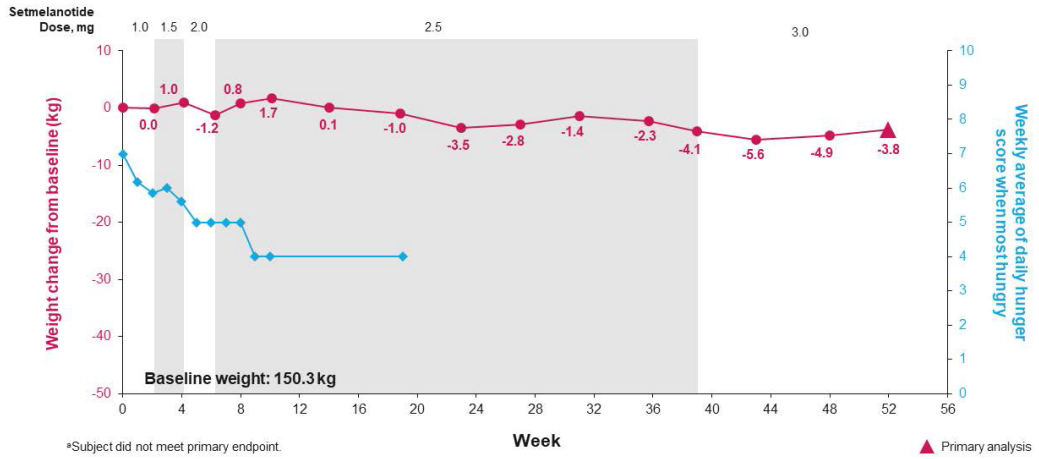
– Percent change in hunger score from baseline: -37.3%

– Did not meet ≥25% decrease in hunger score from baseline

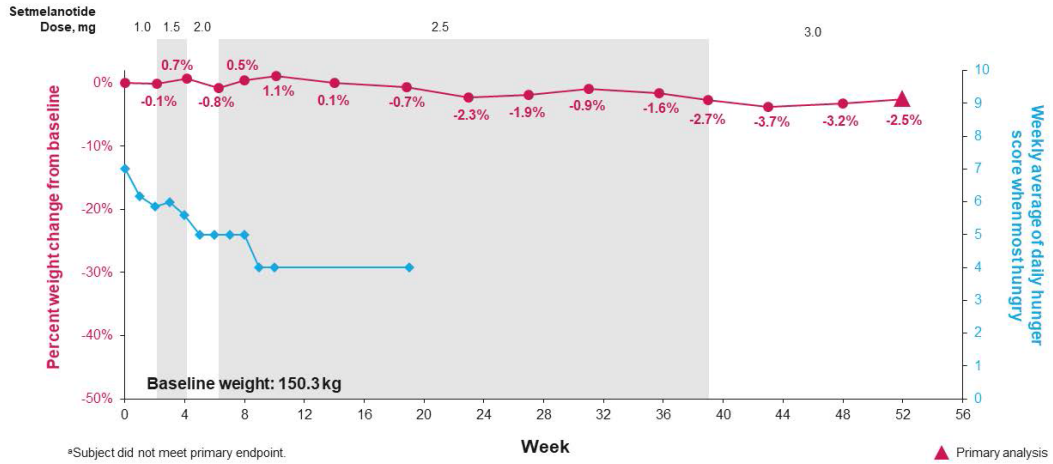
Total Treatment

Over the course of treatment in the study, the patient's body weight decreased from 150.3 to 146.5 kg and hunger score improved from 8.0 to 4.0 (at the last assessment in Week 19). Over this same time period, waist circumference decreased from 142 (screening value) to 139 cm, and BMI decreased from 60.2 to 58.7 kg/m2.

Figure 27. (b) (6) Weight change and weekly average hunger score



[a]Subject did not meet primary endpoint.



[a]Subject did not meet primary endpoint.

Double-Blind, Placebo-Controlled Withdrawal Sequence

Following Open-label Treatment Period 1, the patient did not participate in the Double-blind, Placebo-controlled Withdrawal Sequence.

Safety Results

The most common TEAEs reported were injection site reactions (ISRs); four (4) of 8 TEAEs reported (50%) were ISRs. This patient did not experience any SAEs.

Discussion / Conclusions

This patient did not meet the primary or key secondary efficacy endpoints and also did not meet the weight loss criterion for the DUS. The TEAEs considered related to setmelanotide were generally consistent with those observed in other studies of setmelanotide (i.e., ISRs).

Subject (b) (6):

This is a (b) (6) with LEPR deficiency obesity diagnosed at age 16. The patient's prior medical history included sleep apnea syndrome (not ongoing). The patient had an ongoing medical history of arthralgia (back, knee, ankle), venous insufficiency, asymptomatic hyperuricemia, and vitamin d deficiency. No ongoing comorbidities likely related to obesity were reported.
During the course of the study, the patient received vogalene for nausea, as needed, and microval and luteran as contraception.

Summary Clinical and Laboratory Data:

Parameter	Screening (or first recorded)	End of study*
Weight (kg)	132.3	130.5
BMI (kg/m2)	52.33	51.62
HR (bpm)	82	80
Blood pressure mmHg	127.7/62	113/57.3
Waist Circumference (cm)	138	124
Weekly Hunger Scores (24h)	7	5.25
Fasting Glucose (mmol/L)	4.5	
HBA1c (%)	4.8	4.9
Total Cholesterol (mmol/L)	4.19	3.49
HDL	0.91	0.89
LDL	2.86	2.24
Triglycerides	0.92	0.8

* Data at time of discontinuation

Efficacy Endpoints
Primary Endpoint: Did Not Meet ≥10% Weight Loss
Key Secondary Endpoints:
– Percent change in body weight from baseline: -1.4%
– Percent change in hunger score from baseline: N/A
– Did not meet ≥25% decrease in hunger score from baseline

Total Treatment

Dosing was interrupted for the last week of the titration period due to the TEAE of Grade 1 eosinophilia. This patient, who had a baseline eosinophil count of 0.06×109/L (normal range 0 to 0.5 ×109/L), had an elevated eosinophil count of 0.73×109/L on Day 43. A repeat test performed 1 week later (on Day 49) showed that the eosinophil count had lowered to 0.15×109/L, and after the 1-week interruption, study drug was resumed. By Day 61, the patient's eosinophil count had increased to 0.8×109/L (value not in clinical database). Study drug was permanently discontinued after setmelanotide administration on Day 61.

The patient received setmelanotide at the therapeutic dose for only 1 week, an insufficient duration to assess the patient's response to setmelanotide. Over the course of treatment in the study (i.e., from baseline to the last visit), the patient's body weight decreased from 132.3 to 130.5 kg and hunger score changed from 7.0 to 5.25. Over this same time period, waist circumference decreased from 138.0 to 124.0 cm, and BMI decreased from 52.3 to 51.6 g/m2.

Safety Results

The most common TEAEs reported by the patient were injection site reactions (ISRs); six (6) of 11 TEAEs reported (55%) were ISRs. Additionally, the subject reported nausea, eosinophilia, and post-injection facial flush.

The eosinophilia was considered serious enough to warrant first interruption of study drug and subsequently drug discontinuation. In addition to flushing, TEAEs that occurred in the setting of eosinophilia included injection site erythema and itching. Laboratory values returned to normal range within 1 week of setmelanotide discontinuation.

Discussion / Conclusions

This patient did not meet the primary efficacy endpoint or key secondary endpoints, and treatment was discontinued early due to TEAE of eosinophilia.

Subject (b) (6):

This is a (b) (6) with LEPR deficiency obesity diagnosed at age 14. Ongoing medical history included hypogonadotropic hypogonadism, recurrent painful throat, and rhinitis. Comorbidities likely related to obesity included impaired glucose tolerance.

During the course of the study, the patient received ibuprofen for fever and rhinitis, amoxicillin for rhinitis, mometason and desloratadine to treat allergic reactions at the injection site, ferrofumaraat to treat and prevent anemia, metformin for glucose intolerance, paracetamol for fever, headache, back pain, stomach pain and menstruation pain in the back and stomach, desloratadine to treat a mosquito bite, estradiol/dydrogesteron and ethinylestradiol/drospire for menstruation regulation, and drops to treat ear pain, as needed.

Summary Clinical and Laboratory Data:

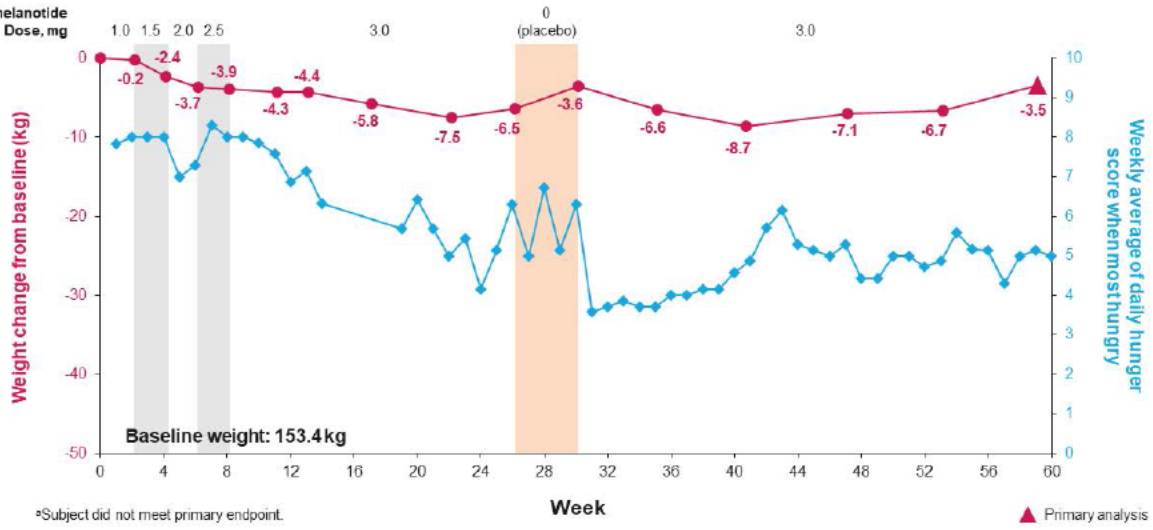
Parameter	Screening (or first recorded)	End of study
Weight (kg)	153.4	149.92
BMI (kg/m2)	49.52	47.85
HR (bpm)	82.7	98.7
Blood pressure mmHg	133.7/72.3	144.7/72.7
Waist Circumference (cm)	149	141.9
Weekly Hunger Scores (24h)	8	5
Fasting Glucose (mmol/L)	3.1	3.9
HBA1c (%)		
Total Cholesterol (mmol/L)	5.7	4.9
HDL	1.28	1.38
LDL	4.17	3.44
Triglycerides	1.55	1.67

Efficacy Endpoints
Primary Endpoint: Did Not Meet ≥10% Weight Loss
Key Secondary Endpoints: – Percent change in body weight from baseline: -2.3%
– Percent change in hunger score from baseline: -37.5%
– Met ≥25% decrease in hunger score from baseline

Total Treatment

Over the course of treatment in the study, the patient's body weight decreased from 153.4 to 149.9 kg and hunger score improved from 8.0 to 5.0. The patient's waist circumference decreased from 149 to 141.9 cm at the last assessment, and BMI decreased from 49.5 to 47.9 kg/m_2 over this time period. The percent change in weight graph was not available in the Applicant's submission for this subject.

Figure 28. (b) (6) Weight change and weekly average hunger score



Double-Blind, Placebo-Controlled Withdrawal Sequence

After receiving placebo for 5 weeks, the patient's weight increased from 147 to 149.9 kg, and (b) (6) hunger score remained 6.3.

Safety Results

The most common TEAEs reported were fatigue (8), headache (6), stomach pain/menstruation pain in stomach (6/4), and injection site reactions (ISRs) (5).
This patient did not experience any SAEs. Other than ISRs, TEAEs of interest were nausea, fatigue and skin hyperpigmentation.

Discussion / Conclusions

Although the patient did not meet the primary efficacy endpoint of 10% weight loss at 1 year, (b) (6) achieved a maximal body weight loss of 5.7% over the course of the study with decrease in hunger scores. The Applicant submission suggested that a compliance issue with the study drug regimen may have been identified in the pharmacokinetics (PK) from this patient with a potentially aberrant setmelanotide concentrations beginning at Visit 5 or 6 and continuing to Visit 12 (including the 8-h PK profiles at Visit 9).

Subject (b) (6):

This is a (b) (6) with LEPR deficiency obesity diagnosed at approximately 5 years of age. The patient's prior medical history included dyslipidemia. Ongoing medical history included hypogonadism, delay in puberty, and urinary incontinence. The patient had no documented ongoing comorbidities likely related to obesity.

At enrollment, this patient was receiving cetura estradiol for puberty induction, desloratadine for a cat and dog allergy and the stamaril vaccine for prevention of yellow fever. These medications were administered concomitantly with setmelanotide throughout the study, with the exception of the vaccine. In addition, the patient received mometason to treat an allergic reaction at the injection site, triamcinolone vascr to treat an allergic reaction, paracetamol for pain, pain after placing orthodontic braces, insomnia and pain due to cholelithiasis, strepsils and tramazolinehydrochloride to treat a common cold, cetura and femoston for puberty induction, diclofenac and ibuprofen for pain due to cholelithiasis, desloratadine for a cat and dog allergy, cefazoline. (b) (6) received the following perioperative medications for a cholecystectomy (b) (6) required during the study: dexamethasone for infection prevention, diclofenac and piritramid for pain, glucose post-surgery, granisetron for nausea, morphine for cholecystitis due to gallstones, propofol, rocuronium and sufentanil as anesthesia and ringer-lactate for bleeding, as needed.

Summary Clinical and Laboratory Data:

Parameter	Screening (or first recorded)	End of study
Weight (kg)	115.47	103.3
BMI (kg/m2)	40.43	35.19
HR (bpm)	76	78
Blood pressure mmHg	117.3/61.7	106.3/56.7
Waist Circumference (cm)	112	107.5
Weekly Hunger Scores (24h)	8	8
Fasting Glucose (mmol/L)	4.1	3.6
HBA1c (%)		
Total Cholesterol (mmol/L)	3.8	4.4
HDL	0.55	0.93
LDL	2.94	3.06
Triglycerides	1.38	1.41

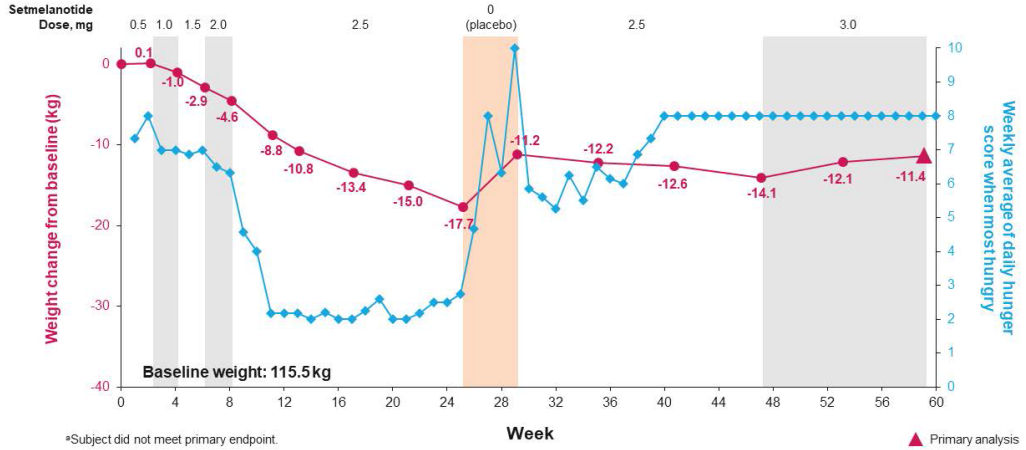
Efficacy Endpoints

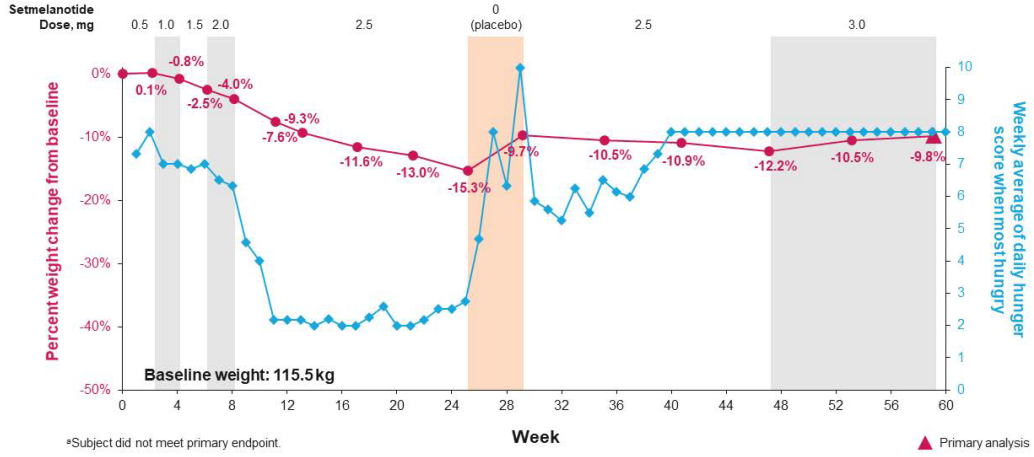
- Primary Endpoint: Did Not Meet ≥10% Weight Loss
- Key Secondary Endpoints:
  - Percent change in body weight from baseline: -9.8%
  - Percent change in hunger score from baseline: N/A
  - Did Not Meet ≥25% decrease in hunger score from baseline

Total Treatment

Over the course of treatment in the study, the patient's body weight decreased from 115.5 to 104.1 kg and hunger score remained at 8.0 at both time points. BMI decreased from 40.43 to 35.19 kg/m2 (13% BMI reduction) and BMIz decreased from 3.66 to 3.12. The patient's waist circumference decreased from 112 to 107.5 cm at the last assessment, and BMI decreased from 40.4 to 35.2 kg/m$_2$ over this time period.

Figure 29. [redacted] (b) (6) Weight change and weekly average hunger score





Double-Blind, Placebo-Controlled Withdrawal Sequence

After receiving placebo for 4 weeks, the patient's weight increased from 97.8 to 104.3 kg, and (b) (6) hunger scores increased from 2.8 to 10.

Safety Results

The most common TEAEs reported by the patient were injection site reactions (ISRs); 6 of 21 TEAEs reported (28.6%) were ISRs. Other events of special interest experienced by this patient included increase in birthmarks and increase pigmentation.
There was 1 reported SAE of cholecystitis due to gallstones reported on Day 216. The patient underwent gallstone removal surgery, and the event was considered resolved on Day 282.
The subject also reported insomnia on two occasions.

Discussion / Conclusions

This patient did not meet the primary or key secondary efficacy endpoints.
Except for ongoing TEAEs related to hyperpigmentation, TEAEs reported were typically mild to moderate in intensity and considered resolved during the study. The TEAEs considered related to setmelanotide were generally consistent with those observed in other studies of setmelanotide (i.e., ISRs, skin hyperpigmentation).

Overall, treatment with setmelanotide led to weight loss of 9.8%, close to the 10% primary outcome threshold. It is important to note this patient gained 3 cm in height and the BMI Z-score changed from 3.66 to 3.12 during the study.

The Applicant submission suggested that a compliance issue with the study drug regimen may have been identified in the pharmacokinetics (PK) from this patient with a potentially aberrant setmelanotide concentrations beginning at Visit 5 or 6 and continuing to Visit 12 (including the 8-h PK profiles at Visit 9)

The subject has several AEs of injection site pain and fear of injection which may have contributed to a compliance issue.

Subject (b) (6)

This is a (b) (6) with LEPR deficiency obesity (diagnostic date unknown).
No medications were reported at baseline. Concomitant medications received during the study included desloratadine and mometasone furoate to treat an allergic reaction at the injection site; paracetamol to treat headache, an ankle injury, and otitis externa; ibuprofen, acetic acid, terracortril med/polymyxin B, and ciprofloxacin to treat otitis externa.

Summary Clinical and Laboratory Data:

Parameter	Screening (or first recorded)	End of study
Weight (kg)	89.37	89.45

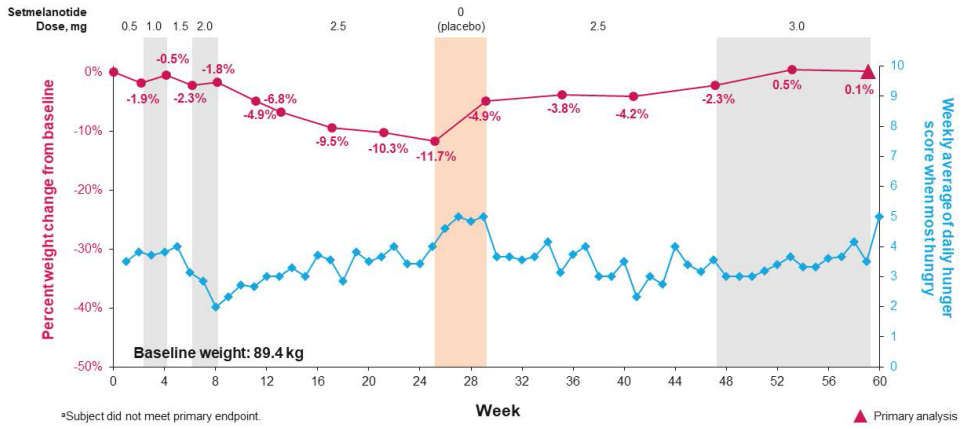
BMI (kg/m2)	36.26	35.83
HR (bpm)	82	75
Blood pressure mmHg	125.7/60	128.3/63.3
Waist Circumference (cm)	104	102.5
Weekly Hunger Scores (24h)	7	5
Fasting Glucose (mmol/L)	3.9	4.8
HBA1c (%)		
Total Cholesterol (mmol/L)	4.4	4.4
HDL	1.98	2.1
LDL	2.53	2.2
Triglycerides	0.95	0.66

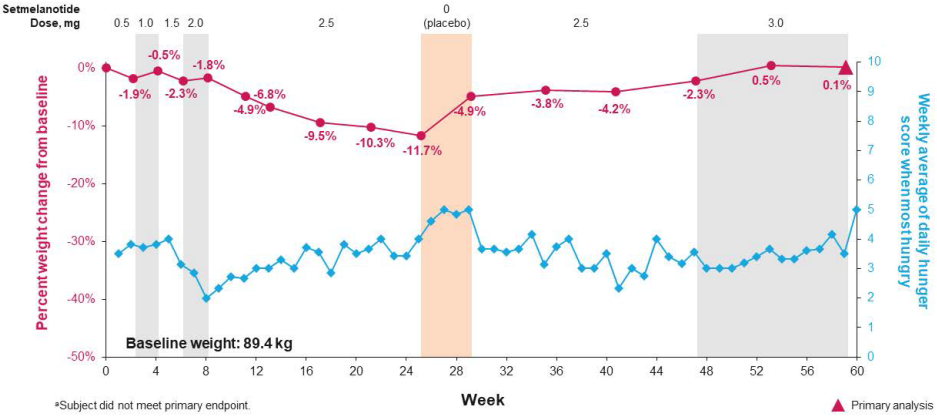
Efficacy Endpoints
Primary Endpoint: Did Not Meet ≥10% Weight Loss
Key Secondary Endpoints:
– Percent change in body weight from baseline: 0.1%
– Percent change in hunger score from baseline: -28.6%
– Met ≥25% decrease in hunger score from baseline

Total Treatment

Over the course of treatment in the study the patient's body weight changed from 89.4 to 89.5 kg and hunger score decreased from 7.0 to 5.0. The patient's waist circumference decreased from 104 to 102.5 cm at the last assessment, and BMI decreased from 36.3 to 35.8 kg/m2 (Z-score 3.11 to 2.99) over this time period. The absolute weight change graph was not available in the Applicant's submission for this subject.

Figure 32. (b) (6) Weight change and weekly average hunger score





Double-Blind, Placebo-Controlled Withdrawal Sequence

After receiving placebo for 4 weeks, the patient's weight increased from 79.0 to 85.0 kg, and hunger scores increased from 4.0 to 5.0.

Safety Results

The most common TEAEs reported by the patient were injection site reactions (ISRs); 10 (10) of 32 TEAEs reported (31.3%) were ISRs, mild to moderate in intensity, and typically lasting 1 day or less. Other TEAEs included headache, hyperpigmentation, gingiva discoloration, sleep paralysis, and malaise.
This patient did not experience any SAEs.

Discussion / Conclusions

This patient did not meet the primary efficacy endpoint but met the key secondary endpoints based on hunger. While being treated with setmelanotide, the patient initially achieved weight loss >10% of 11.5 kg, an 11.7% weight loss from baseline, with an associated decrease in hunger scores from 7 to 4 at the end of Open-label Treatment Period, with this level of weight loss not sustained through the remainder of the study.

Further, following administration of placebo, (b) (6) weight markedly increased. After resuming setmelanotide after the placebo withdrawal period, no further weight loss or consistent improvement in hunger was seen. PK data suggest an issue with compliance with the study drug regimen which may be related to the lack of resumption of weight loss and hunger control after the placebo withdrawal period. Following administration of placebo, (b) (6) hunger and weight gain immediately returned, with little change in (b) (6) weight after resumption of treatment with setmelanotide.

The Applicant submission suggested that a compliance issue with the study drug regimen may have been identified in the pharmacokinetics (PK) from this patient with a potentially aberrant setmelanotide concentrations beginning at Visit 5 or 6 and continuing to Visit 12 (including the 8-h PK profiles at Visit 9)

Subject (b) (6):

This is a 23-year-old Asian female with LEPR deficiency obesity. A prior medical intervention to control weight included placement of an adjustable gastric band, without successfully decreasing weight gain.

Additional ongoing medical conditions included diabetes mellitus, sleep apnea. mild renal impairment with decreased serum albumin and creatinine, idiopathic pulmonary hemosiderosis, and muscular pain.

At enrollment, this patient was receiving Vitamin D to treat vitamin D deficiency, iron and folic acid to treat microcytic anemia, simethicone for gastrointestinal disorders, and magnesium and other dietary supplements. These medications were administered concomitantly with setmelanotide throughout the study.

Summary Clinical and Laboratory Data:

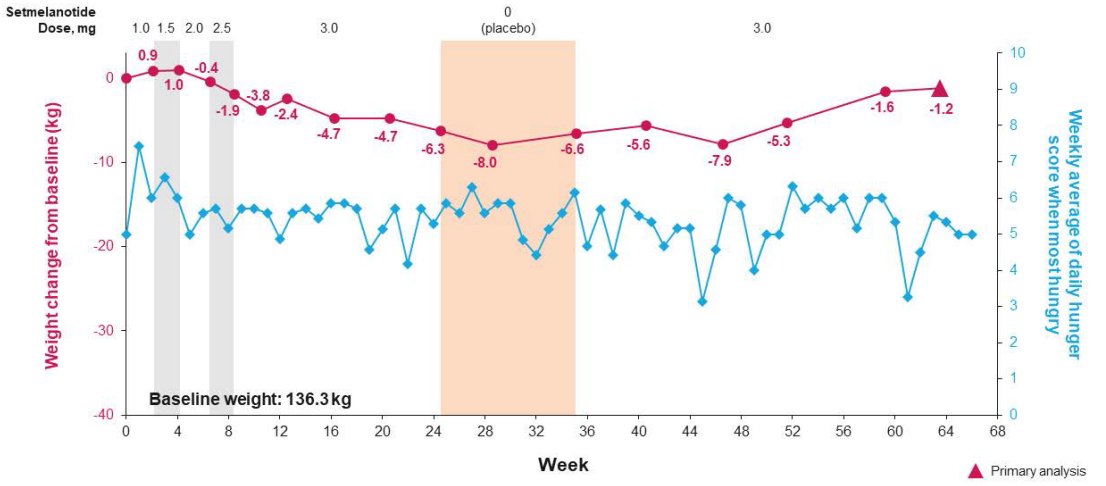
Parameter	Screening (or first recorded)	End of study
Weight (kg)	136.35	134.77
BMI (kg/m2)	46.63	46.09
HR (bpm)	81.3	95.3
Blood pressure mmHg	119.3/61	123.3/72
Waist Circumference (cm)	133	123.6
Weekly Hunger Scores (24h)	5	6
Fasting Glucose (mmol/L)		
HBA1c (%)		
Total Cholesterol (mmol/L)		
HDL		
LDL		
Triglycerides		

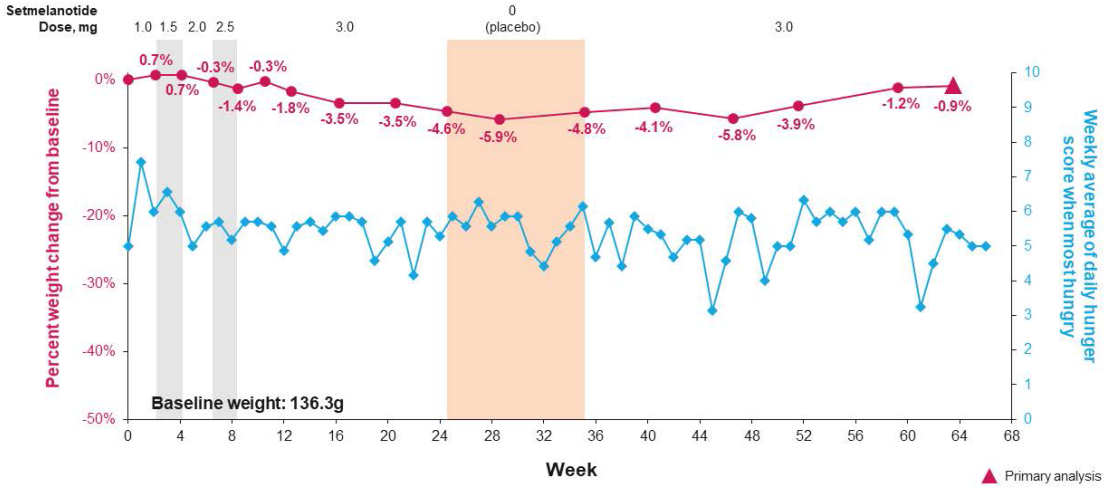
Efficacy Endpoints
Primary Endpoint: Did Not Meet ≥10% Weight Loss
Key Secondary Endpoints:
– Percent change in body weight from baseline: -0.9%
– Percent change in hunger score from baseline: 20%
– Did not meet ≥25% decrease in hunger score from baseline

Total Treatment

Over the course of treatment in the study, the patient's body weight changed from 136.4 to 134.8 kg and hunger score changed from 5.0 to 6.0. The patient's waist circumference decreased from 133 to 123.6 cm, and BMI decreased from 46.6 to 46.1 kg/m2.

Figure 34. (b) (6) Weight change and weekly average hunger score





Double-Blind, Placebo-Controlled Withdrawal Sequence

After receiving placebo for 4 weeks, the patient's weight decreased from 130.1 to 128.4 kg, and hunger scores remained at 5.9.

Safety Results

The most common TEAEs reported by the patient were injection site reactions (ISRs); six (6) of 25 TEAEs reported (24.0%) were ISRs, mild in intensity, with these events being of variable duration from 19 to 200 days. Other TEAEs included skin darkening, anxiety, emotional lability, and heavy vaginal bleeding. This patient did not experience any SAEs.

Discussion / Conclusions

This patient did not meet the primary efficacy endpoint or key secondary endpoints. While being treated with setmelanotide, the patient initially achieved some weight loss which was not sustained. Further, following administration of placebo, there was no clear change in weight or hunger scores, with return to near baseline weight after resumption of treatment with setmelanotide.

Data Quality and Integrity - Reviewers' Assessment

The study was monitored by Rhythm or its designee. Monitoring included on-site review of source documents/CRFs for completeness and clarity, cross-checking with source documents. Clarification of administrative matters was also performed. The review of medical records was performed in a manner to ensure that patient confidentiality was maintained.

The site monitor ensured that the investigation was conducted according to protocol design and regulatory requirements by frequent communications (letter, telephone, and fax).
Regulatory authorities, the IRB/IEC, and/or Rhythm's clinical quality assurance group, or designee, may have requested access to all source documents, eCRFs, and other study documentation for on-site audit or inspection. Direct access to these documents was guaranteed by the investigator at all times in support of such activities.

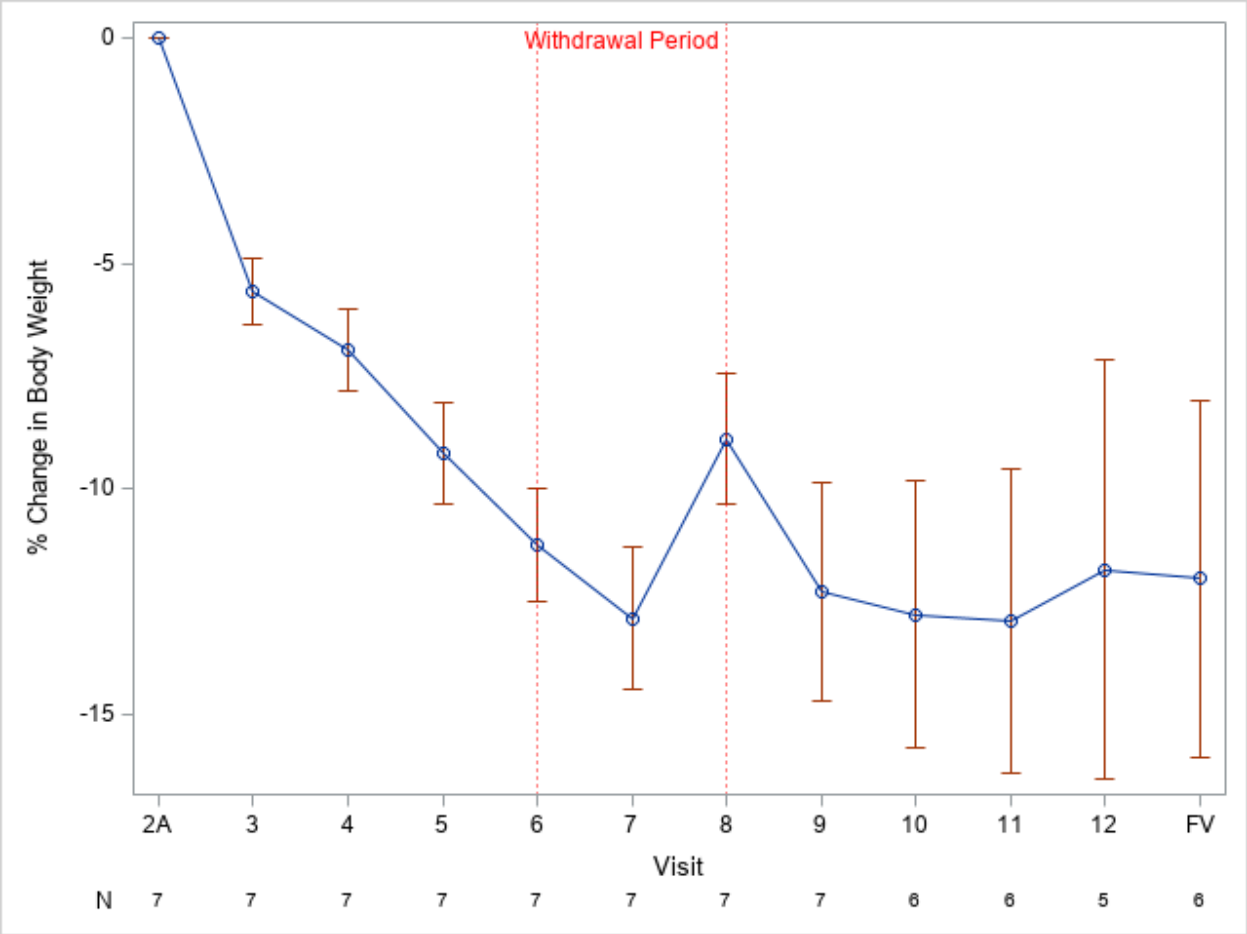
Efficacy Results - Secondary and other relevant endpoints

Mean Percent Change from Baseline in Body Weight in the Pivotal Cohort:

This key secondary endpoint was met. The mean percent change from baseline in FAS was -9.8 (90% CI -14.8, -4.9; p=0.0005) and in DUS -12.8 (90% CI -19.3, -6.3; p=0.0006).

There were two subjects in Study 015 with missing body weight at 1 year: one subject with AE (non-DUS) was imputed as 0 change from baseline. The other subject who died from car accident (DUS) was imputed using multiple imputation and analyzed using Rubin's rule.

Figure 35. Percent Change from Baseline in Body Weight Over Time in the Pivotal Cohort (DUS)



Source: Figure 5 of Applicant's CSR

Mean Percent Change at ~52 Weeks from Baseline in Hunger Score ('Most' Hunger') in the Pivotal Cohort (DUS)

This key secondary endpoint was met. In the pivotal cohort in the DUS population, a LS mean percent change from baseline in hunger score of -41.9% was seen at Week 52 (i.e., after 52 weeks of treatment at the therapeutic dose). However, the assessment tool has significant limitations. Furthermore, interpretation of open-label data in a very limited number of subjects (no data can be used from subjects below 12 years old) and in the context of lack of historical control data is difficult. For details see the clinical outcome assessment review by Dr. Yasmin Choudhry.

The hunger score used in the assessment of endpoints was the daily worst (most) hunger in 24 hours. Daily hunger scores were averaged to determine an average weekly hunger score for

analysis. The average weekly hunger score of the daily worst (most) hunger score in 24 hours is the hunger score used to assess study endpoints.

7 Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

Population characteristics:

Table 8. Patient Demographics-Pivotal Cohort

Characteristics	Study 012 (N=10)	Study 015 (N=11)
Age		
Mean (SD)	18.4 (6.2)	23.7 (8.39)
Min, Max	11, 30	13, 37
Sex, n(%)		
Male	5 (50)	3 (27.3)
Female	5 (50)	8 (72.7)
Race, n(%)		
White	7 (70)	10 (90.9)
Other	3 (30)[1]	1 (9.1)[2]
Ethnicity, n(%)		
Hispanic Or Latino	1 (10)	0
Not Hispanic Or Latino	8 (80)	11 (100)
Unknown	1 (10)	0
Country, n(%)		
USA	1 (10)	0
Non-USA	9 (90)	11 (100)

1. The 3 other races in Study 012 include 1 Arab, 1 Moroccan and 1 NA.
2. The 1 other race in Study 015 is South Asian.

In Study 012, one subject was labeled as discontinued the study due to lack of efficacy. However, the subject only discontinued treatment early and had no missing data for body weight and hunger score measurements at 1 year. In Study 015, one subject discontinued the study at Week 33 due to death from injuries sustained in an automobile accident, which was considered unrelated to study drug. Another subject was withdrawn from the study early at Week 9 due to adverse event (AE) probably related to study drug. In total, 2 subjects had missing data for body weight and 3 subjects had missing data for hunger score at 1 year.

The patients were roughly balanced in sex. Majority of the patients were white, and all except one patient were from USA.

Table 9.0Patient Dispositions

Dispositions	Study 012 (Pivotal Cohort)	Study 012 (Supplemental Cohort)	Study 015 (Pivotal Cohort)	Study 015 (Supplemental Cohort)
Enrolled	10	4	11	2
Treated	10	4	11	2
FAS[1]	10	3	11	2
DUS[2]	9	2	7	1
Safety Set[3]	10	4	11	2
Completed Study, n(%)[4]	9 (90)	0	9 (81.8)	0
Withdrew from Study, n(%)[4]	1 (10)	1 (25)	2 (18.2)	0
Missing Data for Body Weight or Hunger Score at 1 Year, n(%)[4]	0	NA	3 (27.3)	NA

1. Full Analysis Set: definition in Section 3.2.2
2. Designated Use Set: definition in Section 3.2.2
3. Safety set consists of subjects who receive any of the study drug injections and have at least one post-dose safety assessment.
4. Percentages are calculated based on FAS.

7.1.1. Primary Endpoints

Primary and key secondary efficacy endpoints in this study of patients with POMC deficiency obesity were met. Overall, my review of the submitted data, supports the indication of setmelanotide for the treatment of chronic weight management in patients with POMC, PCSK1, or LEPR deficiency obesity in adults and children 6 years of age and older.

(b) (4)

The primary endpoint for this application is the proportion of patients with POMC, PCSK1 and LEPR deficiency obesity that achieves at least 10% weight loss from baseline at 1 year of therapeutic dose of setmelanotide. To support this endpoint the Applicant conducted two similarly designed studies in POMC, PCSK1 and LEPR subjects respectively. For details of study design and individual results see sections 6.1 and 6.2 of this review.

Upon my review of the two supporting studies I concluded that the primary endpoint has been achieved, with 80% of patients with POMC or PCSK1 deficiency obesity meeting the criteria as well as 46% of patients with LEPR deficiency obesity.

This conclusion is supported by the statistical reviewer's analyses as well. The two sensitivity analyses conducted by the statistical reviewer, including a conservative analysis that considered all missing values as non-responders, gave the same conclusion. For details please see the statistical review by Jiwei He, PhD.

Table 10. Primary endpoint: Proportion of Patients Achieving at Least 10% Weight Loss at 1 Year - FAS

Parameter	Statistic	Study 1 (POMC, PCSK1) (N=10)	Study 2 (LEPR) (N=11)
Subjects Achieving at Least 10% Weight Loss at Year 1	n (%)	8 (80.0%)	5 (45.5%)
	95% CI[1]	(44.39%, 97.48%)	(16.75%, 76.62%)
	P-value[2]	<0.0001	0.0001

1. From the Clopper-Pearson (exact) method
2. From exact binomial test, testing the null hypothesis: Proportion =5%.

Source: Clinical Summary of Efficacy Tables 4 and 5, verified by Statistical Reviewer.

The response in POMC, PCSK1 subjects was extremely robust, with virtually all subjects responding to treatment. The two subjects that did not lose weight are outliers, with one being a non-responder in whom a subsequent confirmatory genetic testing demonstrated this patient had a benign genetic variant (POMC / c.158A>G, pAsp53Gly_HOM) and the second being the only PCSK1 subject in the pivotal cohort. Details of both these subjects can be found in section 6.1.2.

7.1.2. Secondary and Other Endpoints

The three key secondary endpoints were: mean percent change in body weight from baseline in the Designated User Set (DUS) population; Mean percent change in weekly average of daily hunger score ('most hunger over the last 24-hours') from baseline in patients ≥12 years of age in the DUS population and subjects that met responder threshold of ≥25% improvement from baseline in hunger threshold (responders) in the FAS population. All 3 secondary endpoints achieved statistical significance.

For the FDA analyses the continuous key secondary endpoints were analyzed in the DUS population. A linear mixed model with a fixed term for time and baseline measurement of weight or hunger score and a random effect for subjects was used and a compound symmetry covariance matrix was employed.

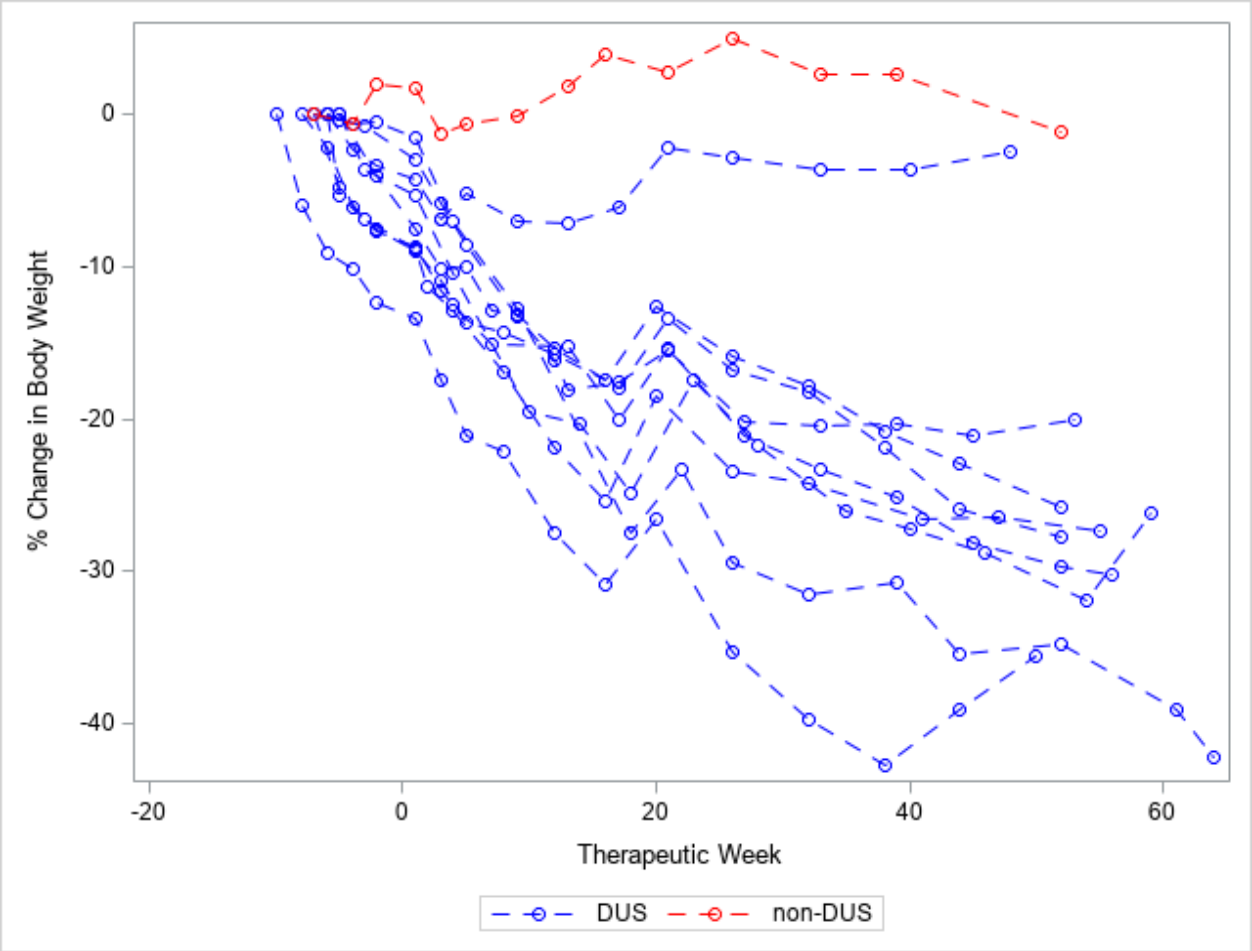
Dr. He performed additional analyses of the continuous endpoints using the FAS population in which she employed an ANCOVA model which included measurements from the final visit at 1 year as the outcome and baseline as a covariate.

Mean percent change in body weight from baseline to 1 year was significantly different from 0 in both the FAS and DUS populations and in both studies, see Table 11. When treatment with setmelanotide was withdrawn in the subjects in the DUS population at round 16 weeks, there appeared to be an increase in body weight in all those subjects, see Figure 36 and Figure 37. Reinitiation of treatment with setmelanotide resulted in resumed weight loss in most of the subjects. The timing of the increase and decrease in body weight matched the starting and ending of the 4-weeks of placebo in the double-blind withdrawal period see Figure 38 and Figure 39.

Table 11 Key Secondary Endpoint 1: Mean Percent Change in Body Weight at 1 Year

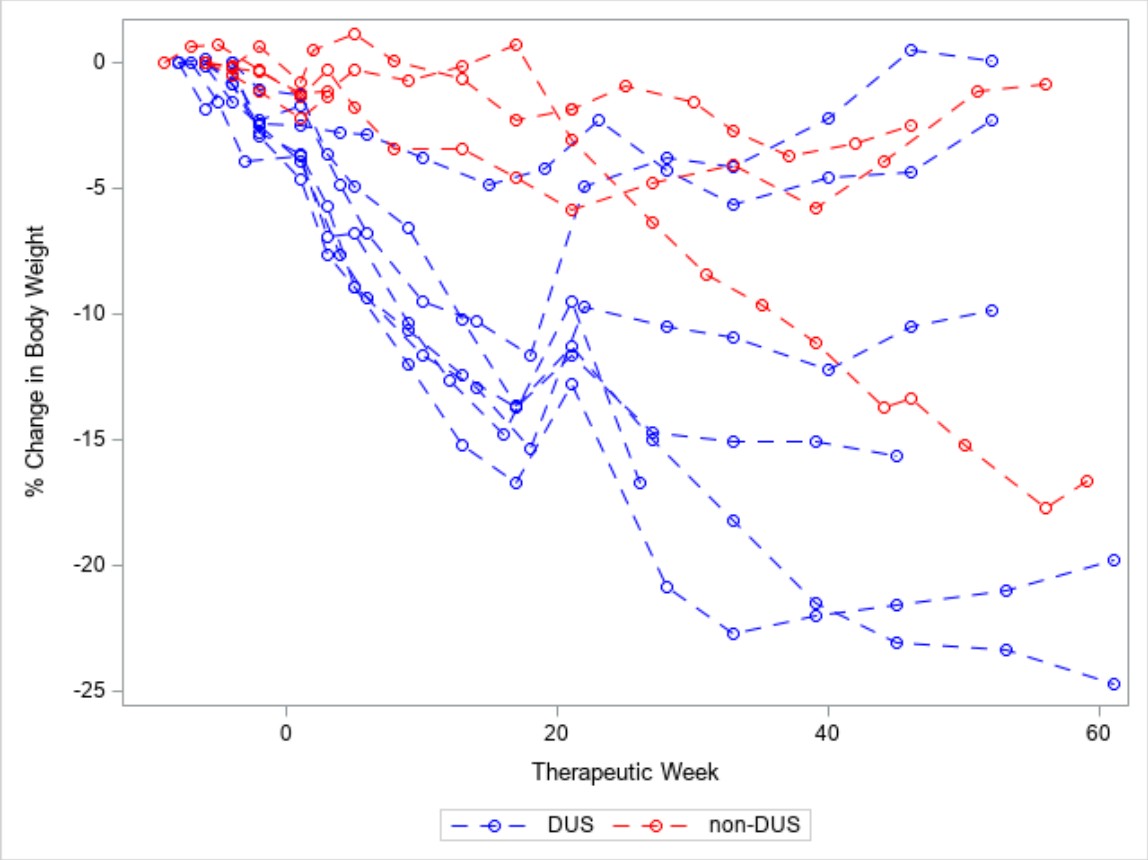
	Study 012 - FAS N=10	Study 015 - FAS N=11	Study 012-DUS N=9	Study 015-DUS N=7
Mean percent change in body weight at 1 year (LS mean)[1]	-23.1	-9.8	-25.6	-12.8
90% CI	(-30.2, -16.1)	(-14.8, -4.9)	(-29.9, -21.2)	(-19.3, -6.3)
95% CI	(-31.9, -14.4)	(-15.7, -4.0)	(-31.0, -20.1)	(-20.5, -5.0)
One-sided p-value[2]	<0.0001	0.0005	<0.0001	0.0006

Figure 36 Percent Change in Body Weight from Baseline in Individual Patients–FAS– Study 012



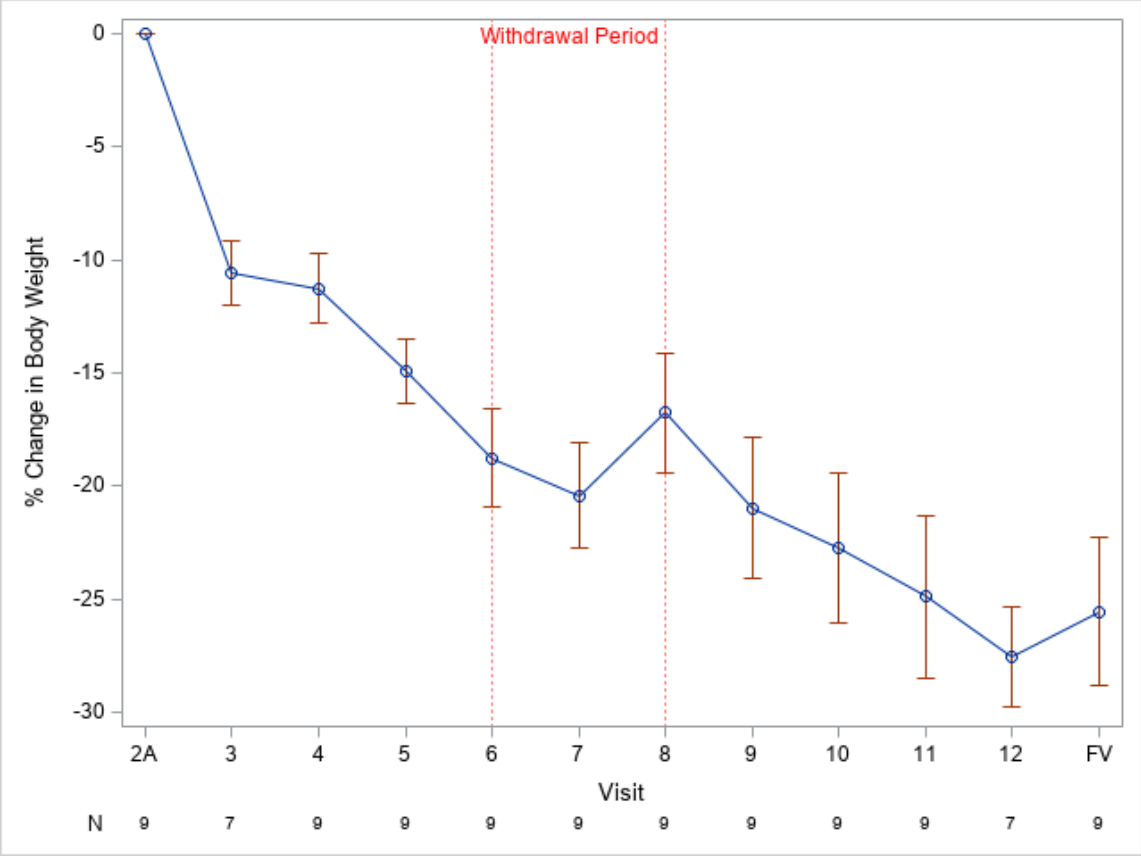
Source: Statistical Reviewer's Analyses

Figure 37 Percent Change in Body Weight from Baseline in Individual Patients– FAS– Study 015



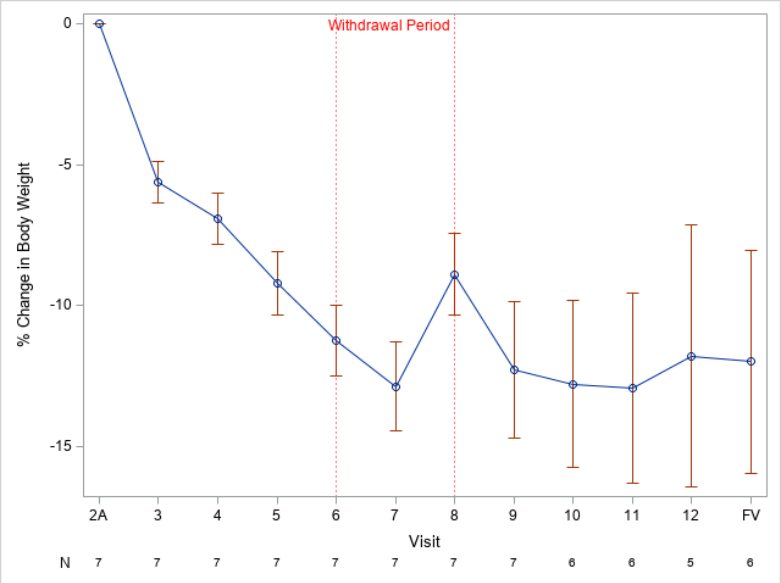
Source: Statistical Reviewer's Analyses

Figure 38 Mean Percent Change in Body Weight from Baseline– DUS – Study 012



2. Error bars represent standard errors. N represents the number of subjects with observed values.
Source: Statistical Reviewer's Analyses

Figure 39 Mean Percent Change in Body Weight from Baseline[1]– DUS – Study 015



1. Error bars represent standard errors. N represents the number of subjects with observed values.
Source: Statistical Reviewer's Analyses

The mean percent change in weekly average of daily "most hunger" score from baseline to 1-year endpoint was also significantly different from 0 in both FAS and DUS populations and in both studies (Table 12). The two sensitivity analyses, including a conservative analysis that considered all missing values as non-responders, gave the same conclusion.

Figure 40. Percent change in Average Hunger Score over 24 hours Study 012

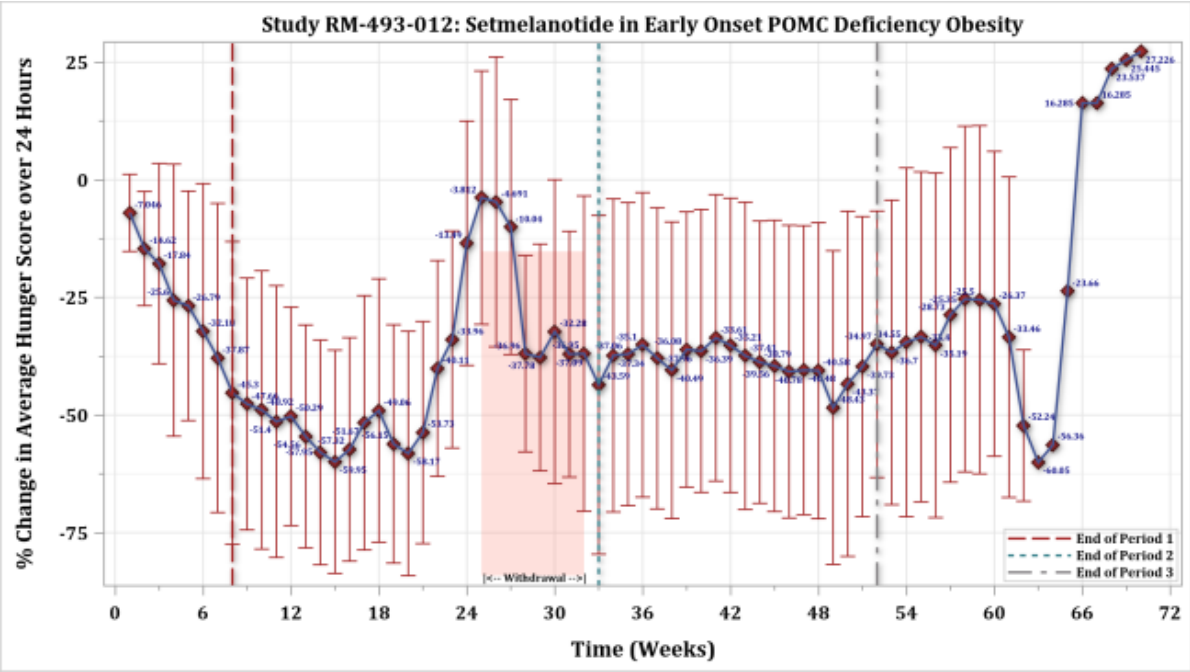


Figure 41. Percent change in Average Hunger Score over 24 hours Study 015

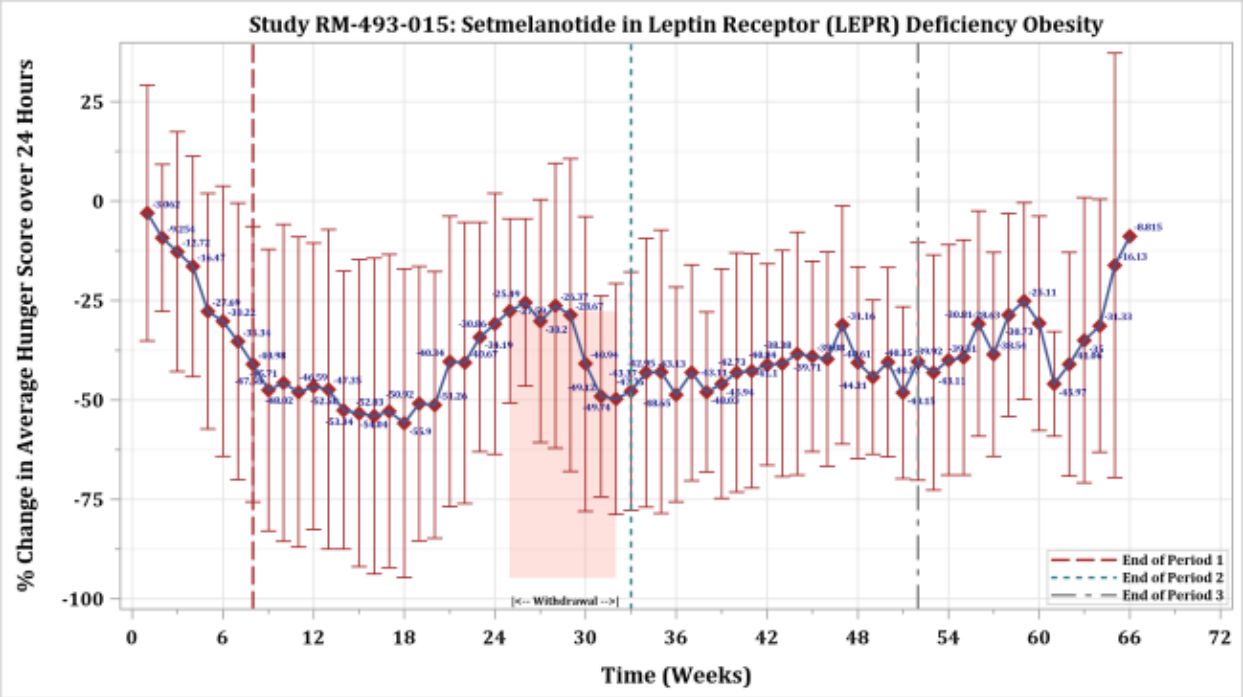


Table 12 Key Secondary Endpoint 2: Mean Percent Change in Weekly Average of Daily 'Most Hunger' Score at 1 Year - **Age≥12** Years

	Study 012 - FAS N=8	Study 015 -FAS N=11	Study 012-DUS N=7	Study 015-DUS N=7
Mean percent change in weekly average "most hunger" score at 1 year (LS mean) [1]	-31.2	-31.0	-27.1	-43.8
90% CI	(-49.0, -13.3)	(-49.4, -12.6)	(-42.6, -11.5)	(-61.5, -26.2)
95% CI	(-53.6, -8.7)	(-53.0, -9.0)	(-46.9, -7.2)	(-64.9, -22.8)
One-sided p-value[2]	0.007	0.003	0.009	<0.0001

1. Linear model contains baseline weekly average 'most hunger' score.
   Three subjects in Study 015 with missing hunger score at 1 year: Two subjects (non-DUS) were imputed as 0 change from baseline. One subject who die from car accident (DUS) was imputed using multiple imputation and analyzed using Rubin's rule.
2. Testing the null hypothesis: mean percent change=0

Source: Statistical Reviewer's Analyses

Statistical reviewer's analyses, and my own, for the hunger score endpoints classified one additional subject as non-responder but did not alter the conclusions from the Applicant's analyses. This key secondary endpoint, although statistically significant is considered clinically

inconclusive due to the issues identified during the Clinical Outcome Assessment (COA) consult review by Dr. Yasmin Choudhry that signaled potential reliability of the patient-reported outcome (PRO) instrument. Specifically, there seems to be substantial lack of data to support whether subjects understood the Daily Hunger Questionnaire Item 2 response scale after migrating from paper to an electronic format as the Applicant did not perform usability testing of the electronic device with patient cognitive interviews to assess device functionality, questionnaire comprehension, and ease of use in the target population. Furthermore, the interpretability of the anchor-based analyses for the Daily Hunger Questionnaire Item 2 is difficult given the small sample size of the studies.

There was significant variability in the subjects' treatment response. This, plus the small sample size due to the rarity of the studied conditions makes the assessment of reliability, validity, and ability to detect change of the used PRO very difficult.

The last key secondary endpoint was the number of subjects that met responder threshold of ≥25% improvement from baseline in hunger threshold (responders) in the FAS population. Results from the Phase 3 studies showed 4 out of 8 patients in Study 012 and 7 out of 11 patients in study 015 achieved at least 25% improvement in hunger score after 1-year treatment of setmelanotide, demonstrating statistical significance (Table 13).

Table 13 Key Secondary Endpoint 3: Proportion of Patients Achieving **≥** 25% Improvement in Weekly Average of Daily 'Most Hunger' Score - **Age≥12** Years; FAS

	Study 012 N=8	Study 015 N=11
Number (%) achieving ≥25% improvement in weekly average 'most hunger' score	4 (50)	7 (63.6)[1]
90% CI[2]	(19.3, 80.7)	(35.0, 86.5)
95% CI[2]	(15.7, 84.3)	(30.8, 89.1)
One-sided p-value[3]	0.0004	<0.0001

1. Three subjects with missing value for hunger score at 1 year: Two subjects (non-DUS) were imputed as 0 change from baseline. One subject who die from car accident (DUS) was considered responder based on linear extrapolation.
2. From the Clopper-Pearson (exact) method
3. From exact binomial test, testing the null hypothesis: Proportion =5%.

Source: Statistical Reviewer's Analyses

While this endpoint was achieved the interpretation of the results in a clinical context is difficult due to the PRO limitations listed above as well as the clinical relevance of the selected endpoints. Furthermore, on review of the cognitive interviews conducted during these studies three of the four patients indicated that a decrease in hunger scores of 3 - 4 points of 9 (33-45%) would be meaningful to them. (b) (4)

Other secondary and exploratory endpoints:

Other efficacy measurements included:
• Reversal of weight and hunger reduction during the double-blind placebo-controlled withdrawal period
• Body composition, including percent change in body fat mass and waist circumference
• Fasting glucose, glycated hemoglobin (HbA1c)
• Fasting lipids (cholesterol and triglyceride)
• Quality of life and health status

Reversal of weight and hunger reduction during the double-blind placebo-controlled withdrawal period

As discussed above during the withdrawal period there was an apparent increase in body weight and hunger scores. See Figure 40 and 41. This supports the mechanism of action of setmelanotide. Same limitations regarding the interpretation of hunger questionnaires applies for this endpoint as previously discussed.

In Study 012 there was a weight loss of 3.0 kg during the 4-week treatment with setmelanotide and a mean 5.5 kg weight gain during the 4-week period receiving placebo: The overall mean change between these 4-week periods was 8.5 kg (p=0.0029).

In Study 015 there was a weight loss of 2.1 kg during treatment with setmelanotide and a mean 5.0 kg weight gain while receiving placebo: The overall, mean change between periods was 7.0 kg (p=0.0014).

Changes in weekly average 'most hunger' score were also compared between treatments during the 8-week placebo-controlled withdrawal period: In Study 012 the mean score was 4.9 during treatment with setmelanotide and 7.1 during treatment with placebo. The mean absolute change in hunger score between the 2 periods was 2.2 units (p=0.1913). In Study 015, the mean score was 3.1 during treatment with setmelanotide and 6.4 during treatment with placebo. The mean absolute change in hunger score was 3.1 units (p=0.0380).

Body composition, including percent change in body fat mass and waist circumference

Patients lost weight and using DEXA measurements, the weight reduction was predominantly loss of fat mass (75% of weight loss in POMC and 67% of weight loss in LEPR was from fat mass loss). No clinical correlation may be considered at this time beyond the effects of dramatic weight loss in this population.

There was a statistically significant and clinically relevant reduction in waist circumference (WC). Baseline Mean WC in study RM493-012 was 119cm (±17.5) and WC following 52 weeks of Setmelanotide the Mean WC decreased to 100.5cm (±12.4). Similarly, in study RM493-015 the WC decreased from 127.3cm (±22.4) to 114.4cm (±20) from baseline to 52 weeks.

Fasting glucose, glycated hemoglobin (HbA1c), Fasting lipids (cholesterol and triglyceride)

A trend towards improvement of glycemic and lipid profile was apparent in the responder population, see Figure 42 and Figure 43, however this cannot be clinically separated from the effects of dramatic weight loss in this population.

Tables 14 and 15 summarize the baseline values for the FAS populations of studies 012 and 015.

Table 14. Metabolic parameters in FAS study RM-493-012

	Cholesterol (mmol/L)	HDL (mmol/L)	LDL (mmol/L)	TG (mmol/L)	Glucose (mmol/L)	HbA1c (%)
Baseline mean value	3.96	1.04	2.28	1.9	7.27	5.8
Mean percent change from baseline	-12.9	19.75	-15.8	-30	-14.2	-15.8

Table 15. Metabolic parameters in FAS study RM-493-015

	Cholesterol (mmol/L)	HDL (mmol/L)	LDL (mmol/L)	TG (mmol/L)	Glucose (mmol/L)	HbA1c (%)
Baseline mean value	4.18	1.1	27	1.4	5.9	5.5
Mean percent change from baseline	-8.14	6.1	-11	-11.3	1.2	-3.6

Figure 42. Change in metabolic parameters in FAS study RM-493-012

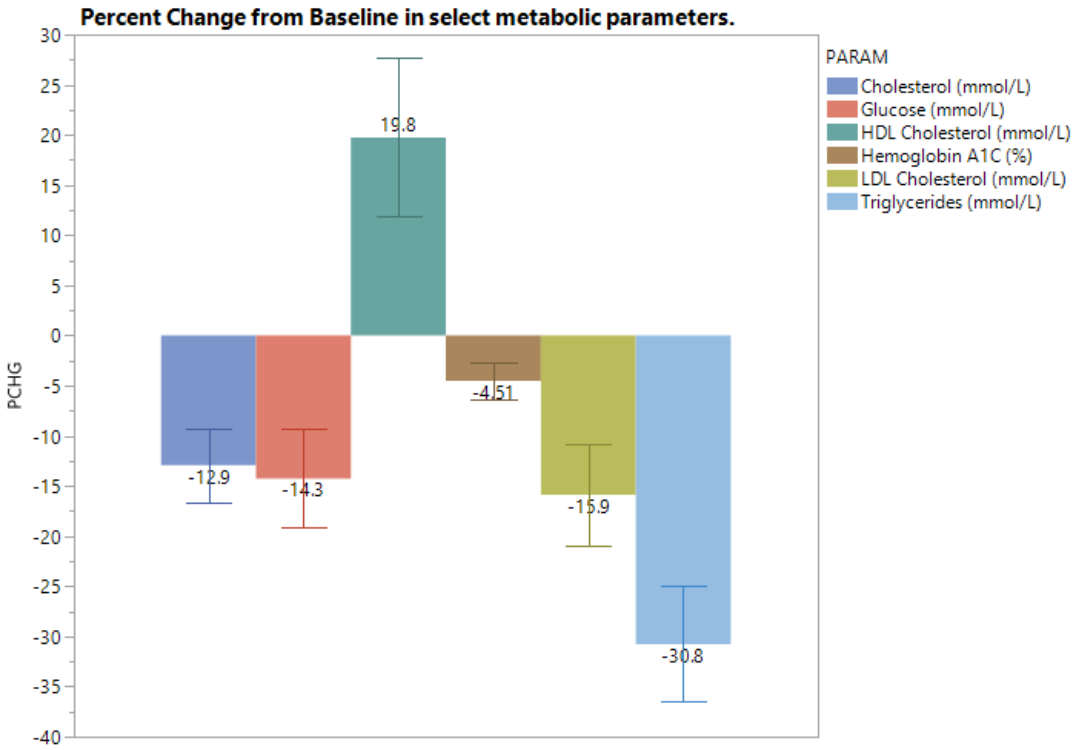
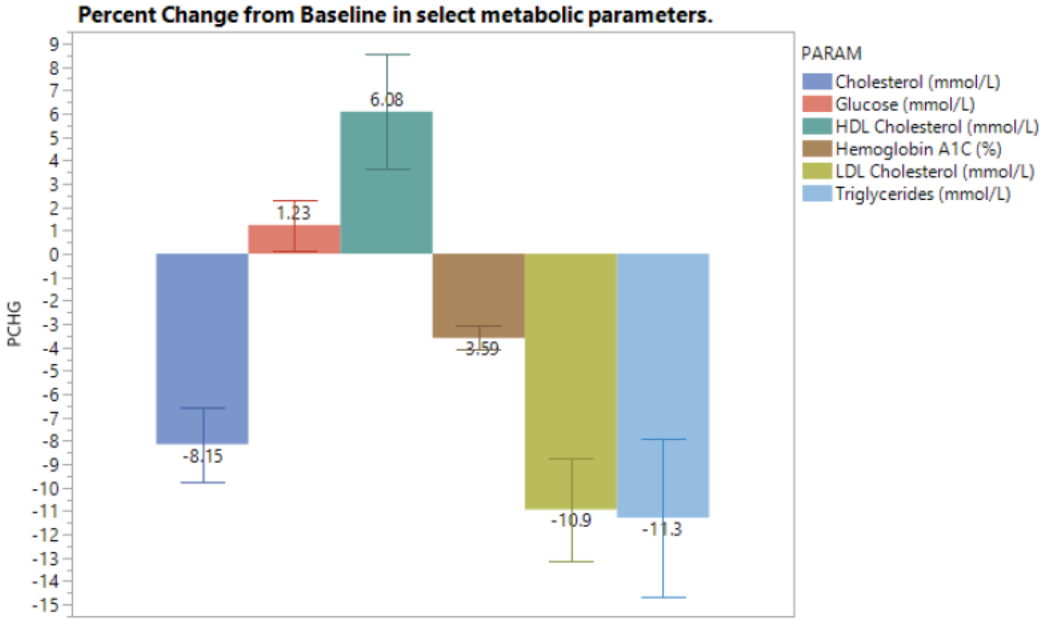


Figure 43. Change in metabolic parameters in FAS study RM-493-015



For the responder population these trends seem consistent at a subject level as well, Figure 44 and Figure 45.

Figure 44. Change in metabolic parameters by subject in FAS study RM-493-012

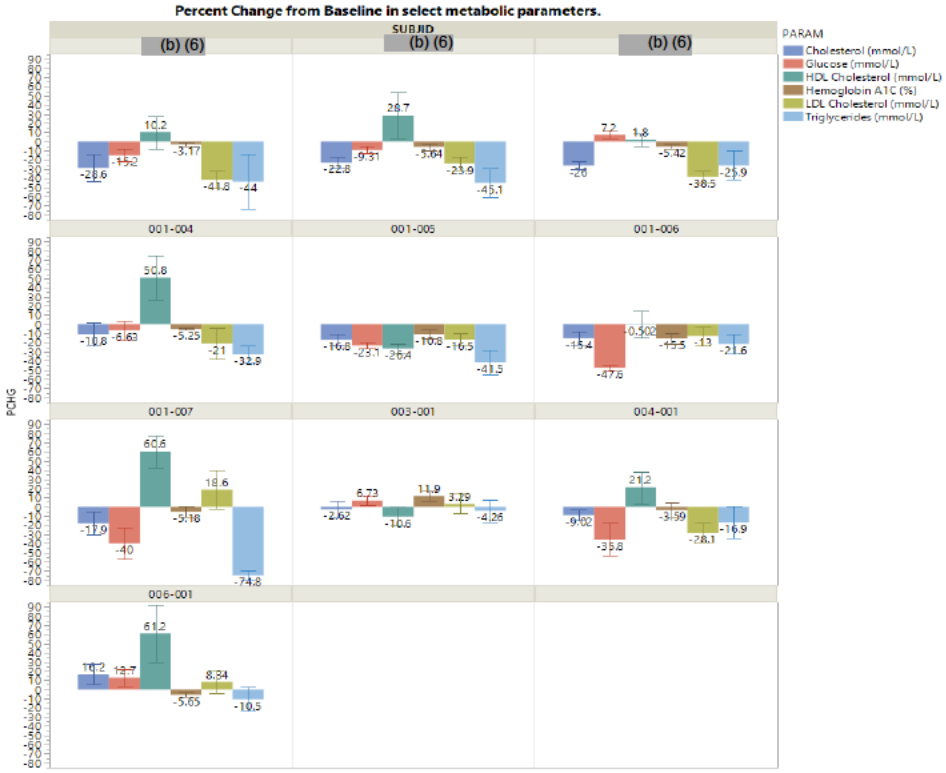
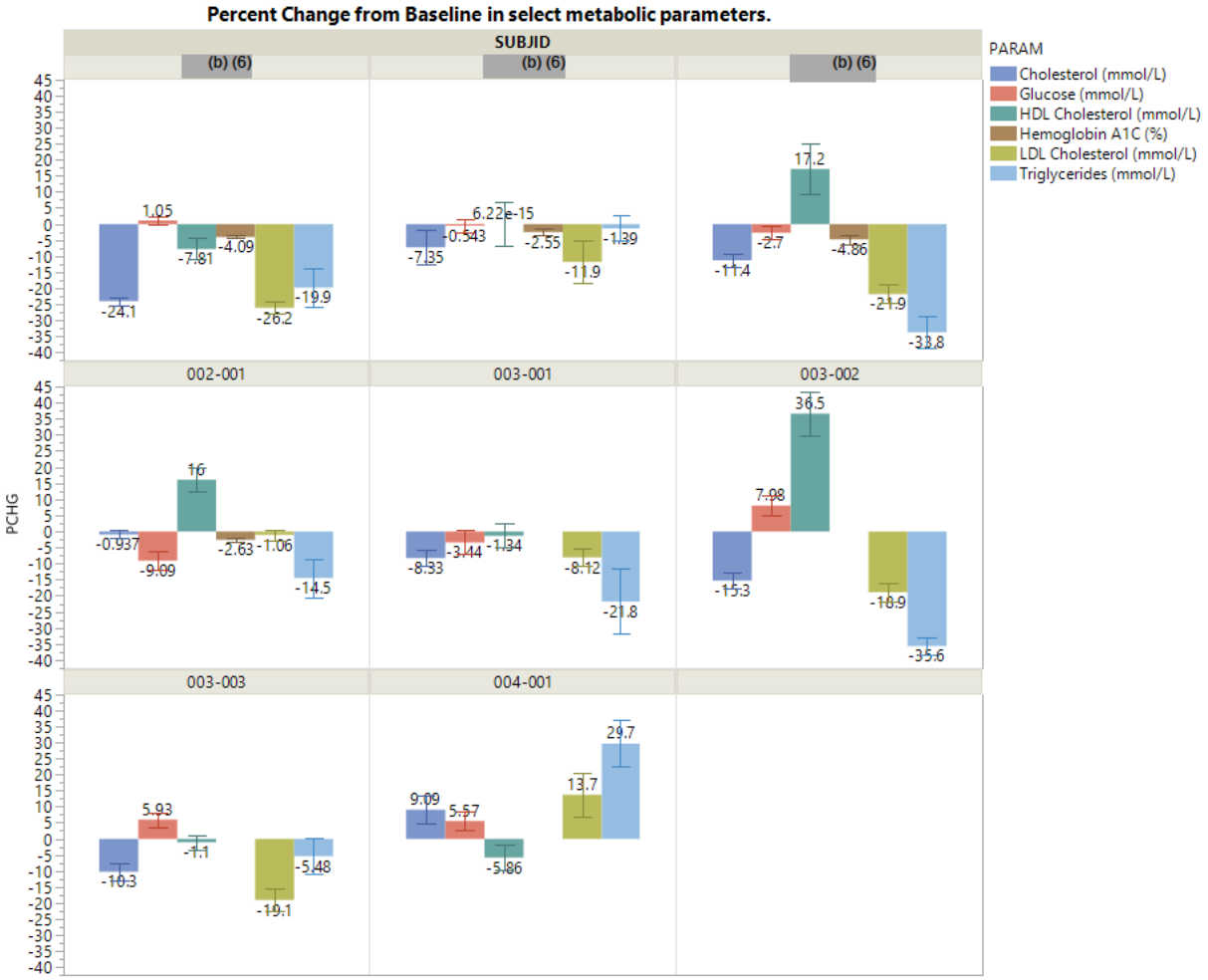


Figure 45. Change in metabolic parameters by subject in FAS study RM-493-015



Quality of life and health status

The general HRQOL measures included the SF-36, SF-10, and PedsQL scales. The condition specific questionnaire administered was the Impact of Weight on Quality of Life (IWQOL). Unfortunately, results for these measures were only available for very few patients due to incomplete data and the use of measures specific to age groups in this small study that included patients from children to adults.

Both study populations had improvements in in health-related quality of life (HRQoL). Due to the limited data these results are hard to interpret at this time.

Subpopulations

Due to the very small sample size in each study, the proportion of responders in the subgroups can vary a lot by chance. However, the primary endpoint was assessed by subgroups,

and is presented as descriptive statistics in Table 14.

Table 14 Subgroup analysis of the primary endpoint - FAS

	% Achieving **≥10%** Weight Loss at 1 Year	
	Study 012 (N=10)	Study 015 (N=11)[1]
Sex, %(n/N)		
Female	80 (4/5)	25 (2/8)
Male	80 (4/5)	100 (3/3)
Race, % (n/N)		
White	85.7 (6/7)	50 (5/10)
Non-White	66.7 (3/4)	0 (0/1)
Age, % (n/N)		
< 18 years	83.3 (5/6)	33.3 (1/3)
≥ 18 years	75 (3/4)	50 (4/8)

1. Two subjects with missing value for body weight at 1 year: one with AE was considered non-responder and the other was considered responder based on linear extrapolation.

Source: Statistical Reviewer's Analyses

7.1.3. Dose and Dose-Response

The proposed starting dose of IMCIVREE is as follows:

(b) (4)

the ClinPharm review concluded that adolescents (12-17 years of age) may benefit from the same starting dose as adult subjects, since their baseline weight is comparable to adults and are predicted to have similar exposures as adults at the same starting dose. No significant safety events of interest were detected in adolescents in clinical trials. As such the recommended starting dose for pediatric patients aged 12 and above was adjusted to the adult dosing on 2mg daily for weeks 1-2 and 3mg daily from week 3 on.

The drug's effectiveness is supported by exposure-response analyses which determined that at the proposed starting and maintenance doses, setmelanotide concentrations were at the plateau of the exposure-response curve. The EC50 (concentration needed to achieve half of the

maximum efficacy = 7.8×10-20 ng/mL) was very small compared to the observed average concentration at the recommended starting and maintenance doses (Cav = 20.62 ng/mL).

Based on the population PK (PopPK) model, using allometric scaling, baseline body weight but not renal function was found to be significant intrinsic covariates associated with setmelanotide exposure. Subjects with mild renal impairment had 19% (-6.5% to 47%) higher setmelanotide steady state AUC compared to those with normal renal function. Similarly, compared to subjects weighing 90 kg, subjects weighting 50kg had 55% (38% - 73%) higher steady state AUC and subjects weighing 200 kg had 45% (39% - 52%) lower AUC.

Due to the strong correlation between age and body weight (younger patients having lower body weight), the applicant's simulations indicated that pediatric subjects tend to be over-exposed compared to adults at the same setmelanotide dose.

A study in hepatically impaired patients was not conducted, and setmelanotide is not indicated in patients with hepatic impairment.

A fixed allometric relationships with exponents of 0.75 (CL/F) and 1.0 (V/F) was included for baseline body weight in the PopPK model. Based on the model and given the distribution of weight in the population PK database, the expected fold-changes in CL/F, relative to a 90 kg patient was a ~35% decrease for a 50 kg patient to an 83% increase for a 200 kg patient. Additionally, the model indicated that age was not a significant factor influencing clearance of setmelanotide, however a strong relationship between age and weight impacts recommendations for pediatric dosing.

For further details please see the Office of Clinical Pharmacology Review.

7.1.4. Onset, Duration, and Durability of Efficacy Effects

Adult dosing in Phase 3 pivotal studies were started at 1 mg, with dose increments of 0.5 mg every 2 weeks, until a therapeutic dose that resulted in weight loss or maximum dose of 3 mg was achieved. The starting setmelanotide dose was 0.5 mg in the pediatric patients (6 to 17 years of age) with dose increments of 0.5 mg and increasing up to a maximum dose of 3 mg. Frequent medical evaluation was needed with these small increments as it took 10 to 12 weeks to achieve a therapeutic dose resulting in weight loss. After the initial open-label period a placebo withdrawal resulted in reversal of weight loss and increase in hunger scores demonstrating the direct correlation between the observed clinical effects and active drug administration.

7.2. Integrated Assessment of Effectiveness

It is my conclusion that the submitted evidence in this application meets the standard for providing substantial evidence of effectiveness to support Setmelanotide for chronic weight management in patients with POMC, PCSK1, or LEPR deficiency obesity in adults and children 6 years of age and older.

For this endpoint the two supporting studies RM493-012 and RM493-015 were well

conducted, had minimal missing data and the review did not identify any issues. See section 6.1 and 6.2 for details.

Despite the limitations of the application, such as the small number of studied subjects and the open-label design of the studies, given the rarity of the studied conditions, it is my conclusion that the data submitted is substantial enough to support approval for this indication. The efficacy of setmelanotide is confirmed by the 80% of the POMC, PCSK1 population and 45.5% of the LEPR deficiency obesity population achieving weight loss of more than 10% at 1 year with an average weight loss of 23.1% body weight in POMC and 9.8% in LEPR. These results are impressive in these specific populations with natural history of continuous weight progression.

Although the secondary endpoints of glycemic control and lipid lowering are not supported by the current application due to limitations discussed previously (see section 7.1.2.) the trend towards normalization of these laboratory parameters demonstrates the importance of weight loss in this population for prevention of comorbidities such as diabetes and cardiovascular disease.

Of note, currently there is no approved therapy for POMC, PCSK1 and LEPR deficiency obesity. Often alternative therapies, including bariatric surgical interventions, are ineffective.

Regarding (b) (4)

8 Review of Safety

8.1. Safety Review Approach

This safety review primarily focuses on the intended-to-treat population of POMC/PCSK1 and LEPR deficiency obesity. Safety data from studies RM493-012 and RM493-015 was evaluated and is presented in section 8.2 of this review. Studies RM493-011 (a Phase 2, open-label, uncontrolled, non-randomized, study with and additional long-term safety extension) and RM493-022 (an extension study of up to an additional 2 years treatment with setmelanotide for patients who had completed a prior study of setmelanotide for genetic obesity disorders upstream of the MC4 receptor in the melanocortin-leptin pathway) were considered, however data from these studies could not be used for the purpose of this review. Details of these studies can be found in section 8.2.

Given the rarity of the studied conditions and the limited number of subjects, I conducted a in depth review of the safety profile of setmelanotide by reviewing individual data and

integrating the safety findings within the context of the disease, subject's prior medical history and the natural progression of the disease.

The Applicant did not conduct clinical trials comparing setmelanotide treatment to placebo or active controls in patients with POMC/PCSK1 and LEPR genetic disorders of obesity. However, they submitted several studies from the development program, including placebo-controlled data. For this reason, my review will also include evaluation of study RM493-009, a Phase 1b/Phase 2a, randomized, double-blind, placebo-controlled study in otherwise healthy obese patients. Study RM493-009 was chosen based on duration of treatment and comparable dose to that indicated in this submission.

The expected therapeutic effects of Setmelanotide, a MC4R receptor agonist, include weight loss, reduction of hunger, and increased energy expenditure. It was important during my review to try to distinguish the weight loss due to therapeutic effect from weight loss due to nausea and vomiting (reported with administration of other therapeutic agents that target the MC4 receptor). Although nausea, vomiting and abdominal pain were reported they were generally mild, transitory and self-limited. As such I concluded that the concern of GI distress confounding the therapeutic effect of Setmelanotide was not justified for this application.

There have been concerns that MC4R agonism may increase blood pressure or cause QT prolongation. Therefore, safety information was also derived from a sub-study of patients from Studies 012, 014, and 015 assessing the impact of Setmelanotide on QT interval. BP and HR were monitored throughout the development program.

Other AEs of interest that were identified during early development of setmelanotide were spontaneous penile erections and female genital arousal, darkening of the skin/ hyperpigmentation (through cross-reactivity with the MC1 receptor).

As with any centrally acting agents, emergence of depression and suicidal ideation was evaluated.

Setmelanotide is formulated for subcutaneous injection, therefore injection site reactions were also considered adverse events of interest.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

A total of 32 subjects were individually evaluated, including 7 that transitioned to the extension study RM-493-022, for the purpose of this review. Of these only 27 could be used due to duration of treatment and/or dosing relevance for the safety evaluation.

Table 15 Exposure to POMC/PCSK1 and LEPR Patients in Setmelanotide Clinical Studies

Study	Total N	Comments
RM-493-011	5	Of the 5 subjects only 1 LEPR subject (SUBJID (b) (6) was treated with doses above 2mg.
RM-493-012	14	4 subjects had exposure <1 year (supplemental cohort)
RM-493-015	13	2 subjects had exposure <1 year (supplemental cohort)

RM-493-022	7	These subjects are duplicates from the other trials and will not be counted in the total.
Total	32	The safety database for this review consists of 28 subjects (14POMC/PCSK1 and 14 LEPR)

Of the safety cohort of 27 subjects, only 18 had exposure to Setmelanotide (2mg or above) of 1 year or more.

Table 16 Duration of Exposure in Subjects Relevant to Safety Review

Number of patients exposed to the study drug: 28	
<12 months	>=12 months
N= 9	N= 18

Table 4 and Table 5, of the Appendix summarize all patients enrolled and disposition as of the data cut off for Studies 012 and 015.

8.2.2. Adequacy of the safety database:

In the context of the rarity of POMC/PCSK1 and LEPR deficiency obesity I found that the safety database is adequate and relevant to this population. The Applicant provided comprehensive records of all subjects. The missing data was minimal, and it was evident throughout my review that efforts were made to ensure adequate follow-up of all subjects, including those discontinued form the studies.
All elements required to make my assessment were present in the Applicant's submission.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

I have not identified any issues regarding data integrity and submission quality. A data fitness assessment was performed in collaboration with the Office of Computational Science (OCS). This comprehensive analysis extended to all submitted trials, however I will focus on the relevant studies for the sought indication.

For study RM493-012 the OCS assessment identified minor issues in the demographics (missing RACE values), and exposure (tx ending after disposition date – likely due to continuation of therapy in the extension study). The AE database analysis showed 2 entries where the AEDECOD was missing. This was manually corrected when construction the safety database used for my review. Minor issues flagged in the laboratory and vital signs were found to not be of any concern for the integrity of this review.

For study RM493-015 assessment identified minor issues in the demographics (missing RACE values), and exposure (tx ending after disposition date – likely due to continuation of therapy in the extension study). The AE database analysis showed 2 entries that were potential

duplicates. I confirmed that Subject RM493-(b) (6) had the AEs of dizziness and nausea starting on day 198 of study that were documented twice. This was corrected in the safety database used for my review. Minor issues flagged in the laboratory and vital signs and other (EKG data) were found to not be of any concern for the integrity of this review.

Study RM493-015 was the only study that reported a fatal outcome. This was reviewed by the OCS assessment and no issues regarding the integrity and adequacy of the submitted information was found. I reviewed the submitted data related to this SAE and found it to be complete.

8.3.2. Categorization of Adverse Events

The Applicant's approach to recording, coding, and categorizing AEs is reasonable and appropriate. Accurate definitions of AEs and serious adverse events (SAEs) were provided in the protocols. All adverse events that occurred after the start of study drug administration were considered treatment emergent adverse events (TEAEs). SAEs were recorded through the Final Study Visit. All adverse events were monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

The AEs were monitored throughout the studies with the information being obtained in the form of non-leading questions (e.g., "How are you feeling?"), and from signs and symptoms detected during each examination, from laboratory evaluation, observations of study personnel, and spontaneous reports from patients as stated in the protocols. All AEs, including injection site reactions and potential systemic reactions were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) grading system.

The protocols contained language providing that all AEs (serious and non-serious) spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination or other diagnostic procedures should be recorded on the appropriate CRF. Any clinically relevant deterioration in laboratory assessments or other clinical findings would be considered an AE and should be recorded on the appropriate CRF. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event. All SAEs that occurred during the course of the study should have been reported by the investigator to the Medical Monitor within 24 hours from the point in time when the investigator become aware of the SAE. All SAEs should have been reported whether or not considered causally related to the study drug. SAE forms should have been completed and the information collected would have included patient number, a narrative description of the event and an assessment by the investigator as to the severity of the event and relatedness to study drug.

Intensity of all AEs including clinically significant treatment-emergent laboratory abnormalities, injection site reactions and potential systemic reactions were graded according to the CTCAE Version 4.0.

Adverse events not listed by the CTCAE were graded as follows:
Mild: discomfort noticed but no disruption of normal daily activity.

Moderate: discomfort sufficient to reduce or affect daily activity.
Severe: inability to work or perform normal daily activity.
Life threatening: represents an immediate threat to life.

Relationship to study drug administration was determined by the investigator according to the following criteria.
None: No relationship between the event and the administration of study drug. The event is related to other etiologies, such as concomitant medications or patient's clinical state.
Unlikely: The current state of knowledge indicates that a relationship to study drug is unlikely or the temporal relationship is such that study drug would not have had any reasonable association with the observed event.
Possible: A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug. The reaction might have been produced by the patient's clinical state or other modes of therapy administered to the patient.
Probable: A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug. The reaction cannot be reasonably explained by the known characteristics of the patient's clinical state or other modes of therapy administered to the patient.

Events of special interest were defined as those either related to TEAEs commonly occurring during treatment with setmelanotide (darkening of skin, sexual events, nausea, vomiting and injection site reactions) or potential mechanistic related events such as hypertension or other events associated with background disease such as depression and suicidal ideation.

During my review of the safety data I concluded that the Applicant's translation of verbatim terms to preferred terms and their categorization of preferred terms was generally adequate. Any discrepancies are addressed below and were found no have no impact on the overall adequacy of the assessment of safety.

8.3.3. Routine Clinical Tests

The safety assessment methods and time points that were described in the protocols seem reasonable and adequate for the population, disease, and indication being investigated. The results of these assessments and any analysis of those results are presented in Section 8.4. For detailed schedules of assessments for the protocols included in the safety analyses please see Appendices.

8.4. Safety Results

8.4.1. Deaths

There is one recorded death in study RM493-015. Subject RM493-(b) (6), was a (b) (6) with LEPR deficiency obesity diagnosed at age 27 that passed away due to

injuries sustained in an automobile accident. The subject was a passenger. (b) (6) had completed week 33 in the study prior to (b) (6) death. For details about the subject's clinical course throughout the study please see section 7.1.
No other fatal events were recorded throughout the evaluated studies.

8.4.2. Serious Adverse Events

A list of SAEs can be found in Table 17.

On review of the SAEs flagged by the Applicant minor issues arose. In Study 012 there were two SAEs of "depression" and "major depression" that were coded separately. For the purpose of my review, I have combined these SAEs.

In Study 015 subject (b) (6) had a SAE of "suicidal ideation" documented, however the subject's "depression" was not considered an SAE. Clinically, severe suicidal ideation is a symptom of severe depression and as such I added the depression event to the SAE list for this subject. Of note this subject had two separate SAEs of "suicidal ideation"; both events were classified as unlikely related to drug administration by the investigator.

Table 17. Serious Adverse Events

Study	SAE	N=11 (100%)
RM-493-012	*Endocrine disorders*	1(9%)
	Adrenocortical insufficiency acute	1 (9%)
	Infections and infestations	1(9%)
	Pneumonia	1 (9%)
	Psychiatric disorders	3(27.2%)
	Depression	2 (18.2%)
	Panic attack	1 (9%)
	Respiratory, thoracic and mediastinal disorders	1(9%)
	Pleurisy	1 (9%)
RM-493-015	*Hepatobiliary disorders*	1(9%)
	Cholecystitis	1 (9%)
	Injury, poisoning and procedural complications	1(9%)
	Road traffic accident	1 (9%)
	Psychiatric disorders	2(18.2%)
	Suicidal ideation	1 (9%)
	Depression	1(9%)
	Surgical and medical procedures	1(9%)
	Gastric banding reversal	1 (9%)

All SAEs were considered unrelated to drug by the investigators and Applicant. Due to the small number of patients reporting an SAE, exposure adjusted and event rates over time are not appropriate to display.

The Applicant's assessment of the depression and suicidal ideation events in these studies was that patients with severe obesity are known to have both depression and suicidal ideation and behaviors therefore the background rate of depression and suicidal ideation in these studies is not unexpected. However, in my review I considered these events potentially related to drug, especially given the fact that Setmelanotide is a centrally acting substance. More details are discussed in section 8.4.4.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

In Study 012 two subjects withdrew from the study; however, no subjects discontinued or withdrew due to AEs.

In Study 015 there were 2 subjects that discontinued/withdrew drug due to AEs. Subject (b) (6) died in a motor vehicle accident. Subject (b) (6) was withdrawn from the study due to Grade 1 eosinophilia, which was considered by the Investigator to be probably related to study drug. This AE was not considered a SAE by the investigator and Applicant.

8.4.4. Significant Adverse Events

For my analysis of significant adverse events, I looked at any AEs that resulted in an intervention, including withdrawal of drug treatment, dose reduction, or significant additional concomitant therapy, including hospitalization.

Table 18 Significant Adverse Events

Study	Subject	AE	Intervention/Action	Comment
RM-493-012	(b) (6)	Injection site reaction	Subject was retrained on self-administration	
		Depression	Psychiatrist visit and subsequent hospitalization	Subject also has AE of "tiredness" flagged as resulting in an intervention, however this was likely in the context of depression
		Pneumonia	Hospitalization	
		Darkening of nevi	Selected nevi were excised	Likely drug related, however there is no evidence of malignant potential of these pigmented lesions with setmelanotide treatment
		Upper respiratory infection	Hydrocortisone dose doubled	Consistent with the natural history of POMC deficiency
		Acute adrenal insufficiency	Hospitalization	Consistent with the natural history of POMC deficiency

	(b) (6)			
		Upper respiratory infection	Administration of IV hydrocortisone and fluids Setmelanotide was interrupted	Consistent with the natural history of POMC deficiency
		Pleuritis	Hospitalization	
		Depression	Hospitalization	Classified in database as major depression
		Medication administration error resulting in overdosing	Setmelanotide was interrupted	
		Panic attack	Hospitalization	This AE was classified as mild, however it resulted in hospitalization.
RM-493-015		Depressed mood	Dose decreased	
		Asthenia	Dose decreased	
		Hyperhidrosis	Dose decreased	
		Suicidal ideation	None	There were 2 identical separate AEs on days 292 and 417
		Gastric band reversal	Hospitalization to remove gastric ring Drug was interrupted	
		Eosinophilia	Dose decreased then drug was interrupted	Subject had 3 consecutive AEs of eosinophilia
		Cholecystitis		

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

As discussed previously all AEs were considered TEAEs and will be presented as one. See table 19

Table 19 Treatment Emergent Adverse Events by Preferred Term in order of frequency occurring in >10% of patients (Safety Population) – Study 012 and 015, Pivotal and Supplemental Cohorts

Preferred Term	N=27	Percent (%)
Injection site reaction[a]	26	96.4
Skin hyperpigmentation[b]	21	77.8
Nausea	15	55.5
Headache	11	40.7
Diarrhea	10	37.0
Abdominal pain[c]	9	33.3
Back pain	9	33.3
Fatigue	8	29.6
Vomiting	8	29.6
Depression[d]	8	29.6
Upper respiratory tract infection	7	25.9

Preferred Term	N=27	Percent (%)
Spontaneous penile erection[e]	3	23.1
Arthralgia	5	18.5
Asthenia	5	18.5
Dizziness	4	14.8
Dry mouth	4	14.8
Dry skin	4	14.8
Insomnia	4	14.8
Vertigo	4	14.8
Alopecia	3	11.1
Chills	3	11.1
Constipation	3	11.1
Influenza-like illness	3	11.1
Muscle spasm	3	11.1
Pain in extremity	3	11.1
Rash	3	11.1
Suicidal ideation	3	11.1
[a] Includes injection site erythema, pruritus, edema, pain, induration, bruising, hypersensitivity, hematoma, nodule, and discoloration [b] Includes skin hyperpigmentation, pigmentation disorders, skin discoloration [c] Includes abdominal pain and upper abdominal pain [d] Includes depressed mood [e] n = 13 male patients		
Source: FDA Clinical Reviewer		

Overall, Setmelanotide was well tolerated with the most common AEs being injection site reactions, skin and hair hyperpigmentation and headache and GI disorders (nausea, vomiting). Generally, these AEs were mild and self-limited.

The most common AEs were injection site reactions that included induration, bruising, erythema, edema, pain, pruritus, bleeding, hematoma (96% of subjects) and hyperpigmentation (78%). In the limited placebo control trial from Study 009 the overall injection site reaction was higher in the Setmelanotide group (71%) than placebo (30%). These are expected AEs for SQ administration and did not lead to major compliance issues, discontinuation of drug or withdrawal from the study.

Skin hyperpigmentation was reported by 78% of subjects and was an expected AE given the coactivation of MC1R by Setmelanotide. This is a benign AE in my opinion with no significant clinical impact. The darkening of nevi may be worrisome for patients, however there is no evidence of progression towards malignancy of these skin lesions. In fact, evidence suggests that MC1R activation in melanocytic nevi may have a protective role by increasing eumelanin synthesis, which quenches reactive oxygen species (ROS) and reduces the generation of DNA damage upon UV exposure. Activation of the cAMP pathway also enhances the DNA repair and

antioxidant capacities of melanocytes. The cumulative outcome of these effects is maintenance of genomic stability of melanocytes.[8]

GI disorders were also common, with 68% of subjects experiencing one or more GI-related AE such as nausea (56%), diarrhea (37%), abdominal pain (33%), vomiting (33%), or constipation (11%). These AE's were of special interest during my review. I considered GI distress to be a potential confounding factor in the assessment of efficacy of Setmelanotide regarding weight loss. However, the reported GI disorders AEs were generally mild, self-limiting and short in duration. Furthermore, there seemed clustering of these events at drug initiation and dose increases and a decrease in reports further into the studies which may suggest development of tolerance.

Fifty percent of subjects had musculoskeletal and connective tissue disorders related AEs, primarily back pain (33%), arthralgia (19%) and muscle spasms (11%). Similarly, 50% of subjects had Nervous system AEs, with headache being the most prevalent (40.7%). While these AEs may not be easily explained by Setmelanotide administration, they are frequent complaints in the general population and may be associated with weight loss. Overall these AEs were mild and short in duration.

Psychiatric disorders represented an AE area of interest and my analysis showed 46% of subjects exhibiting a related AE. The most common reported psychiatric AEs were depression (30%) and insomnia (15%). Suicidal ideations were also prevalent with 11% of subjects having at least one such AEs reported. Furthermore, these psychiatric events were often (5 of 13) serious or classified as events of interest by the investigators and often resulted in hospitalization, dose reduction. Additionally, in the limited placebo control data available from Study 009, 3 (5%) subjects reported depression in the setmelanotide group vs 0 in placebo. This data is limited and represents short exposure to drug.

These AEs and their severity represent a concerning finding. While the baseline mental health of the studied population may be poor, it is my opinion that the potential of an increase in depression and suicidal ideation with Setmelanotide treatment needs to be signaled to the providers and patients through adequate labeling.

8.4.6. Laboratory Findings

[8] Swope, V Abdel-Malek, Z "MC1R: Front and Center in the Bright Side of Dark Eumelanin and DNA Repair" Int J Mol Sci. 2018 Sep

Overall, no trends or clinically meaningful changes were observed in clinical laboratory assessments throughout the studies. There were no discernable patterns of shift from baseline for abnormal hematology parameters, liver and kidney functions, urinalysis parameters or coagulation parameters.

Slight variations in mean laboratory values were observed; however, the changes were generally minor and not considered clinically significant.

The datasets used for my analysis of laboratory data were the adlb.xpt files from the respective studies. For ease of analysis data from RM493-011 was modified to only consist of laboratory data for subject (b) (6).

For details regarding glucose and insulin, lipid profile, coagulation, hematology, chemistry and urinalysis see Tables 14.4.1.2, 14.4.1.2.1, 14.4.1.7, 14.4.1.1, 14.4.1.2, 14.4.1.3 and 14.4.1.4 Applicant's submission for study RM493-012 and Section 12.4 of CSR for Study RM493-015.

8.4.7. Vital Signs

Setmelanotide was evaluated extensively for CV parameters, primarily for the potential concern of MC4R agonism effects on BP and HR. The available data give rise to no concerns regarding increases in 'office' or ambulatory BP, changes in HR or changes in circadian variation of those parameters, during treatment with setmelanotide.

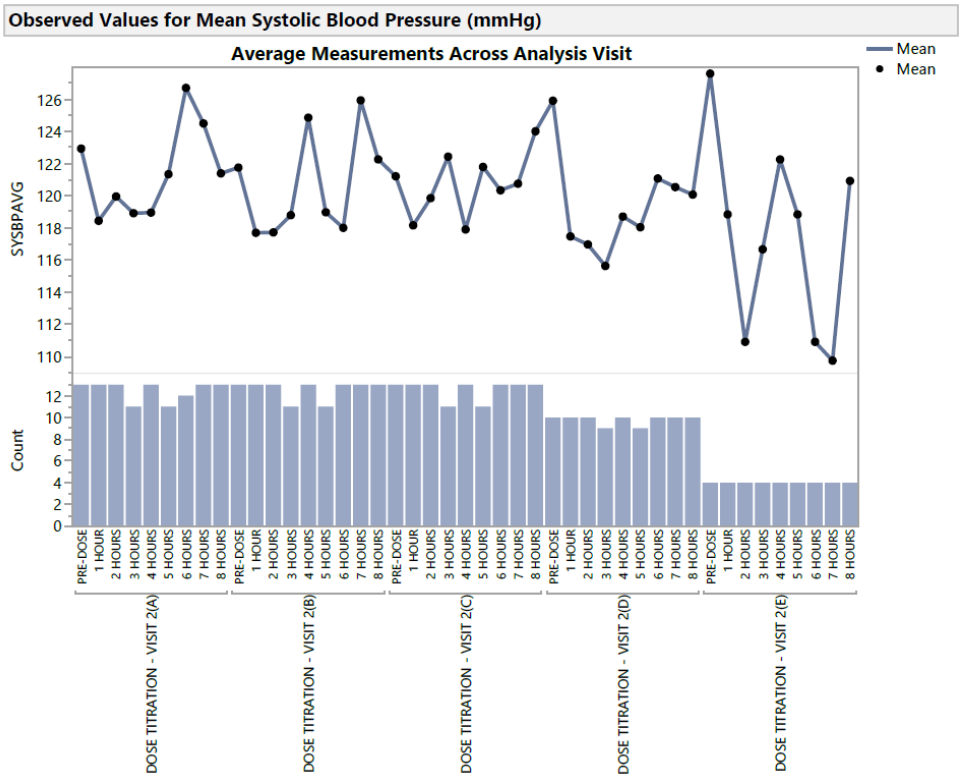
8.4.8. Ambulatory Blood Pressure Monitoring (ABPM)

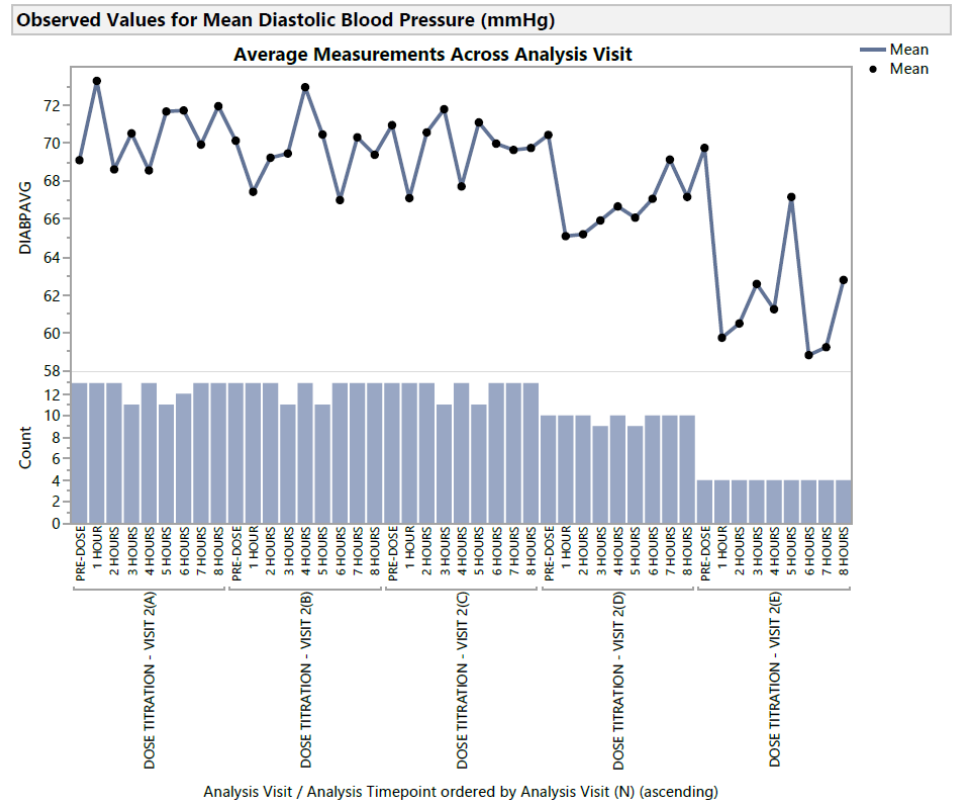
In Phase 1 and 2 clinical trials (RM-493-002, RM-493-003, and RM-493-009), 150 patients underwent CV evaluations, most including 24-hour Ambulatory Blood Pressure Monitoring (ABPM). According to the Applicant's analysis there was little if any signal of BP or HR increases following dosing at 2.5, 12 and 25 mg/kg/day. Additionally, the applicant concluded that there was no evidence of a PK/PD relationship for blood pressure or heart rate.

The applicant also reported on ABPM and 'office' BP and HR data collected in Studies 012, 014, and 015. Office BP and HR data were collected from a total of 57 subjects across the three studies, and ABPM data were collected from a subset of 15 of these subjects. The applicant concluded that the summary data of the ambulatory BP and HR show no overall tendency for heart rate or blood pressure to increase after 85 and 365 days of treatment. The office BP and HR also did not demonstrate systematic increase in office BP during the studies, with upper 95% confidence intervals of the mean changes being about +5 mmHg for systolic and +2 mmHg for diastolic pressure. Similarly, the upper and lower 95% confidence intervals of the change in office HR were under ±6 bpm.

For the two pivotal studies reviewed there were no concerning signals regarding the ABPM findings. BP and HR generally remained stable or trended down during dose titration. BP and HR trended down over the course of the study compared to baseline.

Figure 45 Study RM-493-015 Mean SBP, DBM and HR




Observed Values for Mean Diastolic Blood Pressure (mmHg)
Average Measurements Across Analysis Visit
Mean
Mean
DIABPAVG
Count
PRE-DOSE
1 HOUR
2 HOURS
3 HOURS
4 HOURS
5 HOURS
6 HOURS
7 HOURS
8 HOURS
DOSE TITRATION - VISIT 2(A)
DOSE TITRATION - VISIT 2(B)
DOSE TITRATION - VISIT 2(C)
DOSE TITRATION - VISIT 2(D)
DOSE TITRATION - VISIT 2(E)
Analysis Visit / Analysis Timepoint ordered by Analysis Visit (N) (ascending)

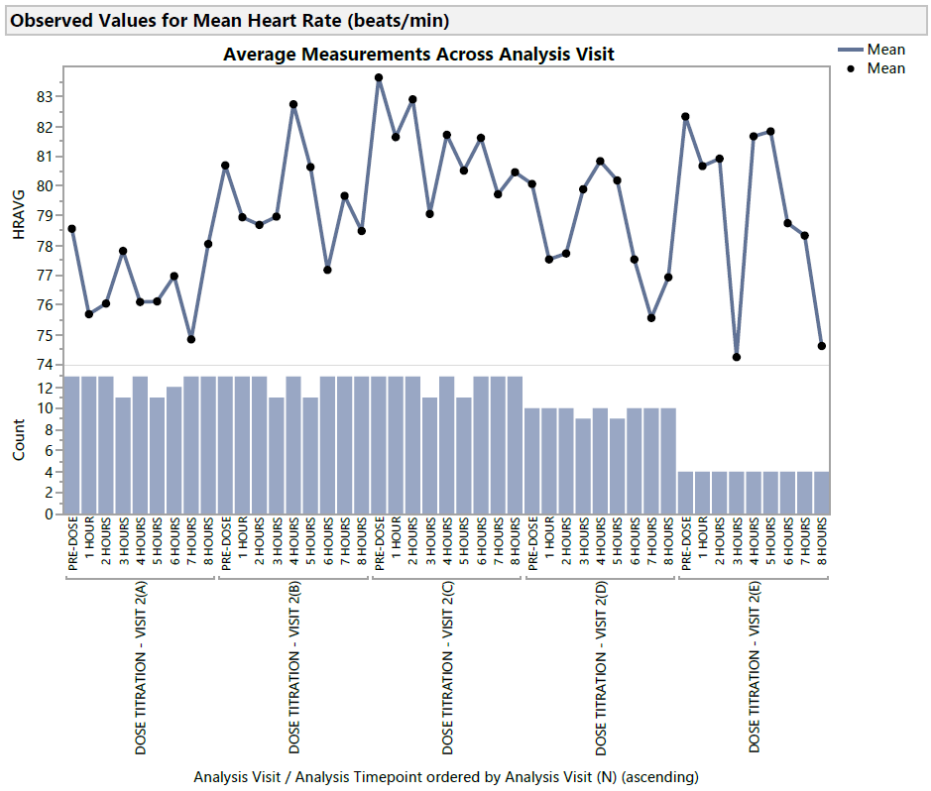
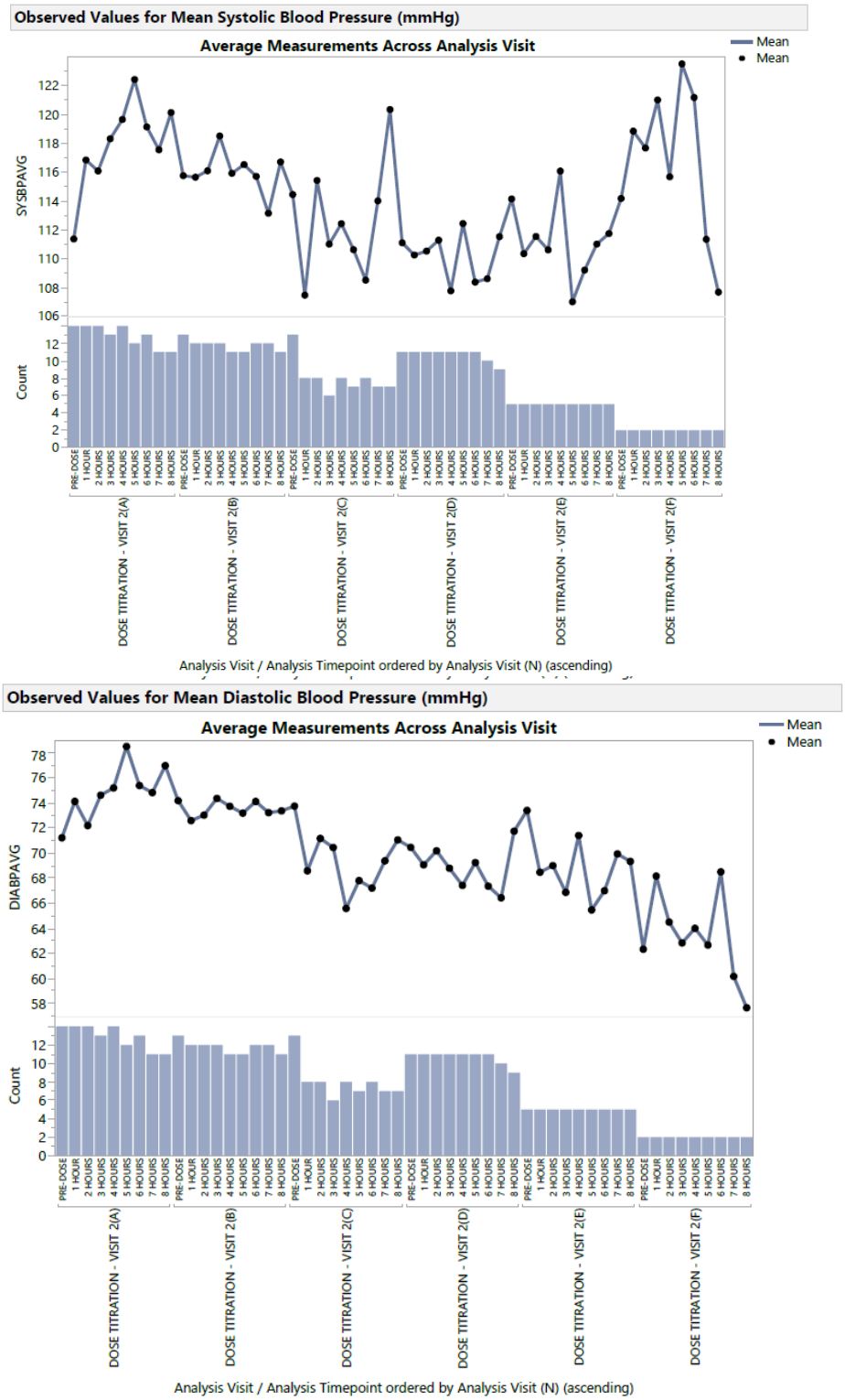
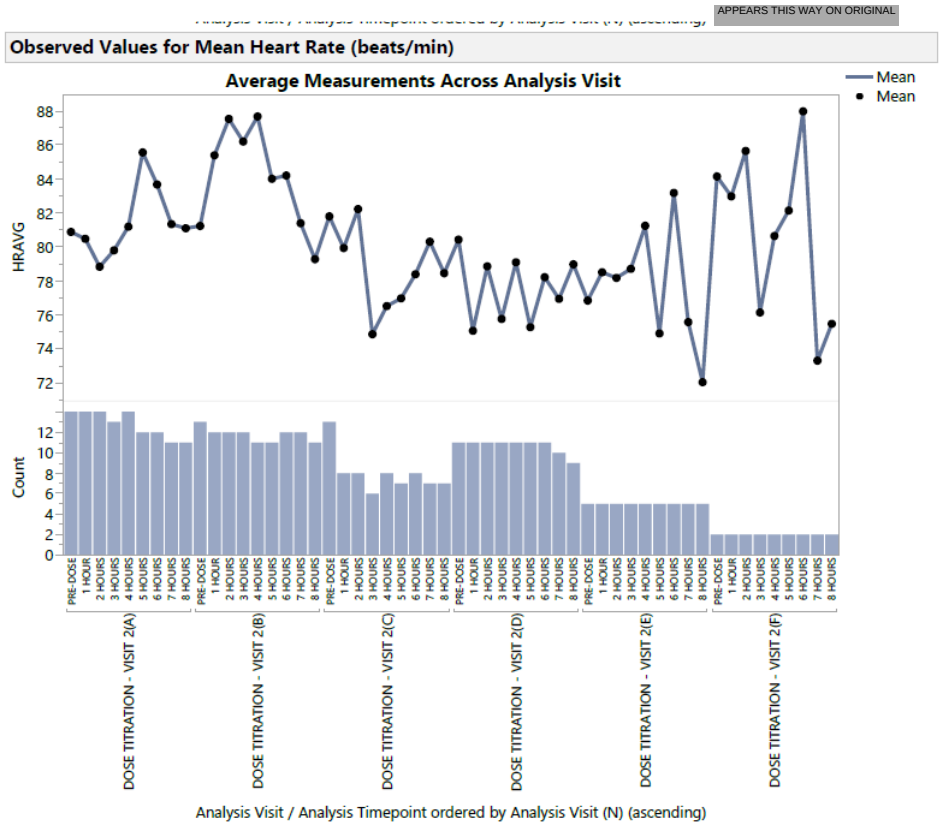
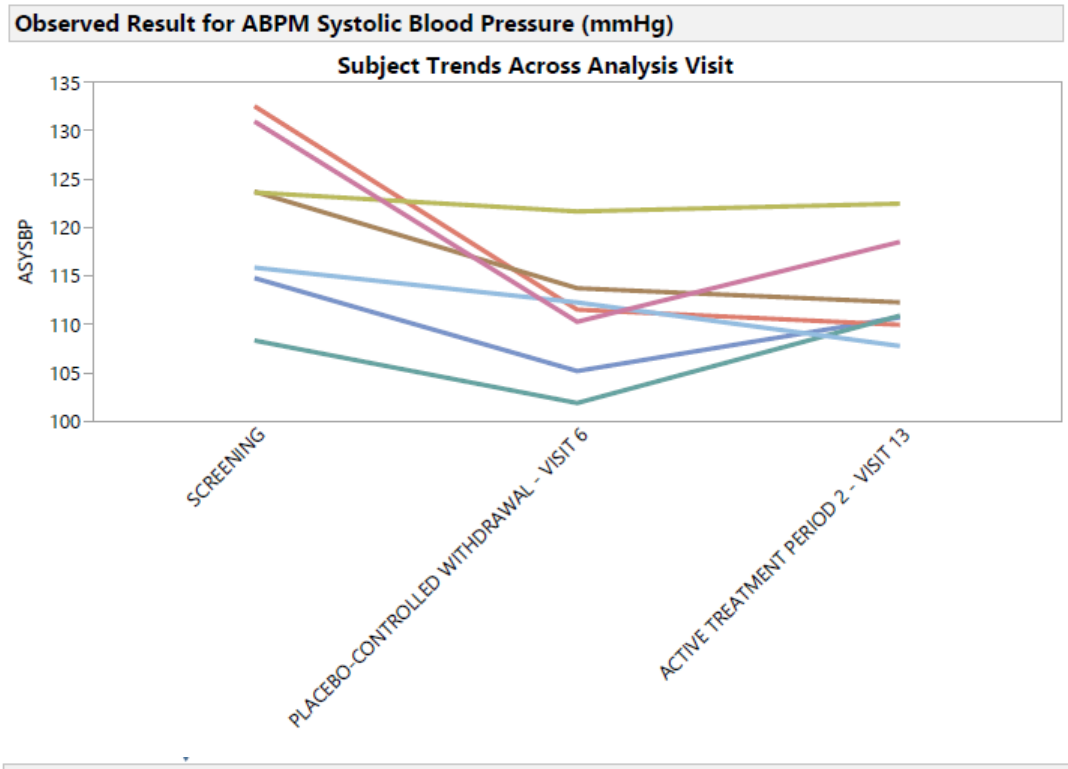

Observed Values for Mean Heart Rate (beats/min)
Average Measurements Across Analysis Visit
Mean
Mean
HRAVG
Count
PRE-DOSE
1 HOUR
2 HOURS
3 HOURS
4 HOURS
5 HOURS
6 HOURS
7 HOURS
8 HOURS
DOSE TITRATION - VISIT 2(A)
DOSE TITRATION - VISIT 2(B)
DOSE TITRATION - VISIT 2(C)
DOSE TITRATION - VISIT 2(D)
DOSE TITRATION - VISIT 2(E)
Analysis Visit / Analysis Timepoint ordered by Analysis Visit (N) (ascending)

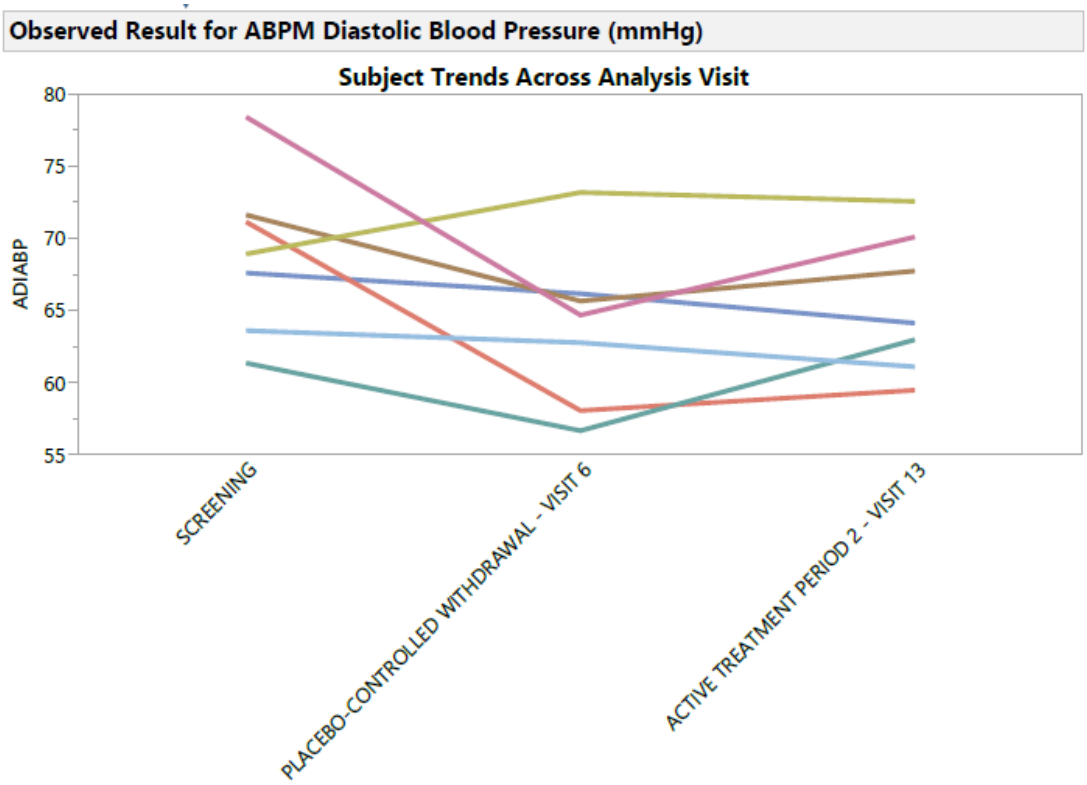
Figure 46 Study RM-493-012 Mean SBP, DBM and HR





Similarly, the subject level analysis did not identify any significant increase in SBP, DBP or HR.
Figure 47 Subject level data Study RM-493-012


Observed Result for ABPM Systolic Blood Pressure (mmHg)
Subject Trends Across Analysis Visit
ASYSBP
135
130
125
120
115
110
105
100
SCREENING
PLACEBO-CONTROLLED WITHDRAWAL - VISIT 6
ACTIVE TREATMENT PERIOD 2 - VISIT 13


Observed Result for ABPM Diastolic Blood Pressure (mmHg)
Subject Trends Across Analysis Visit
ADIABP
80
75
70
65
60
55
SCREENING
PLACEBO-CONTROLLED WITHDRAWAL - VISIT 6
ACTIVE TREATMENT PERIOD 2 - VISIT 13

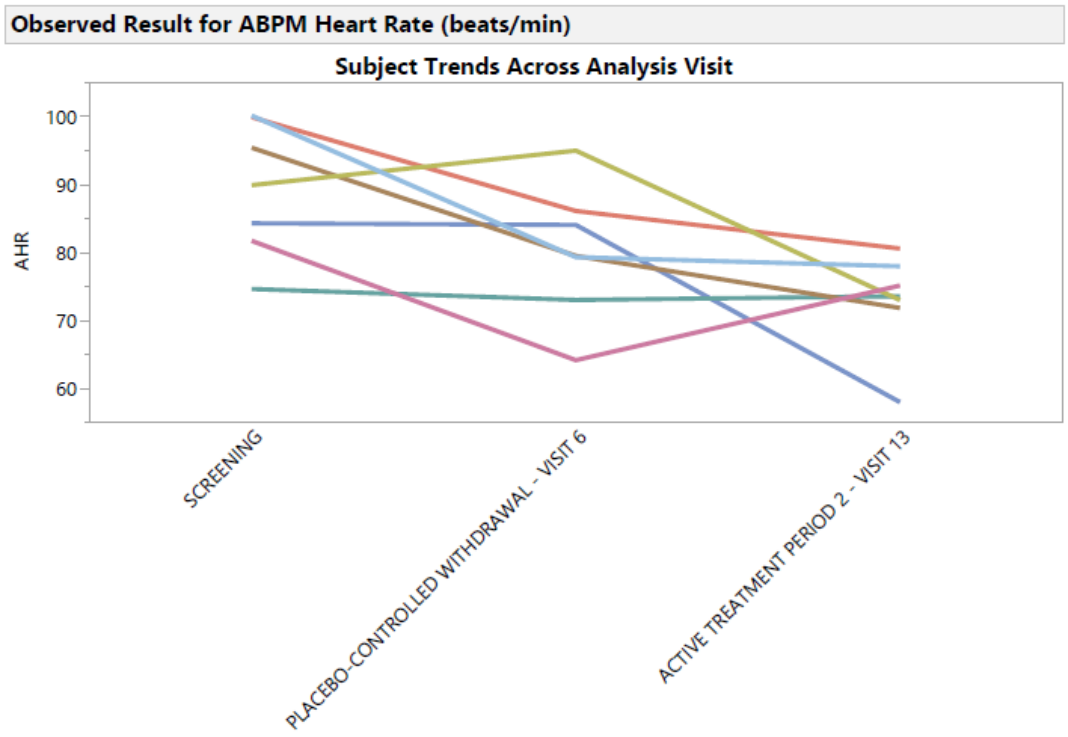
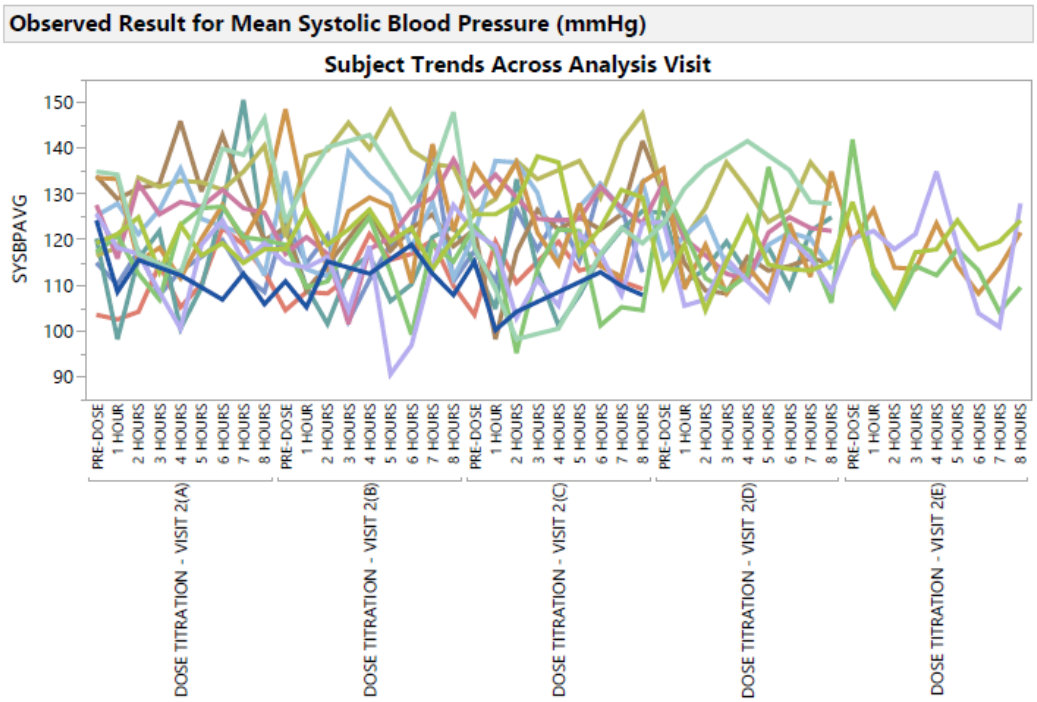
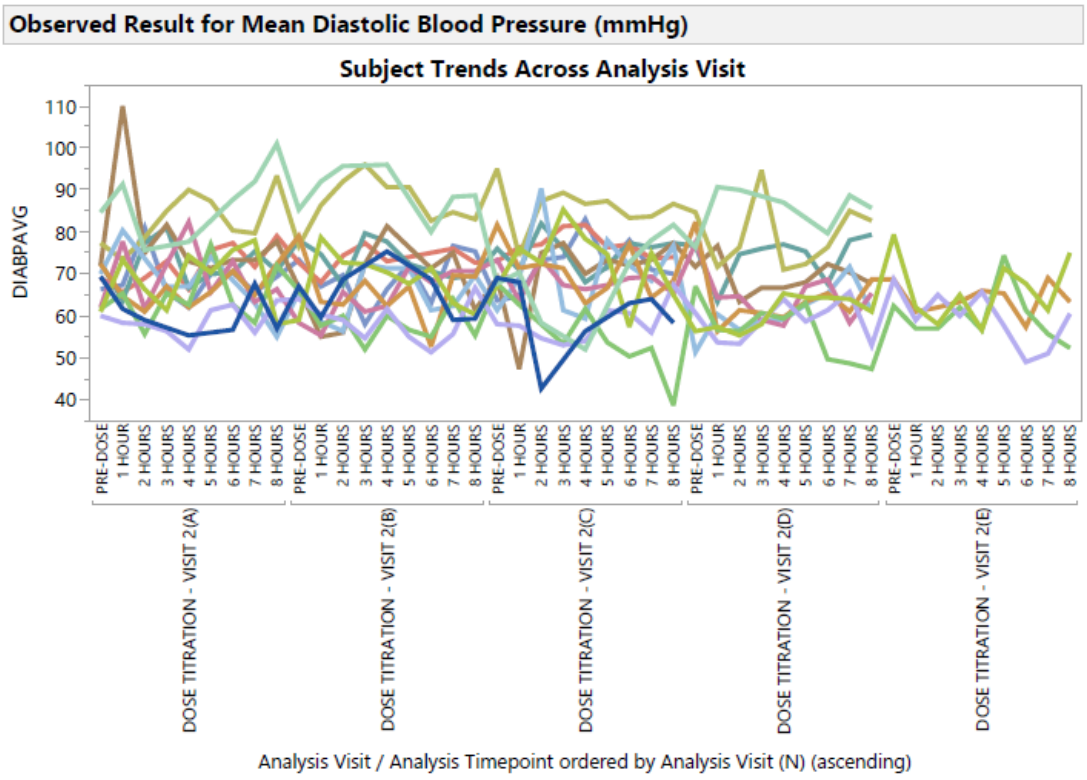
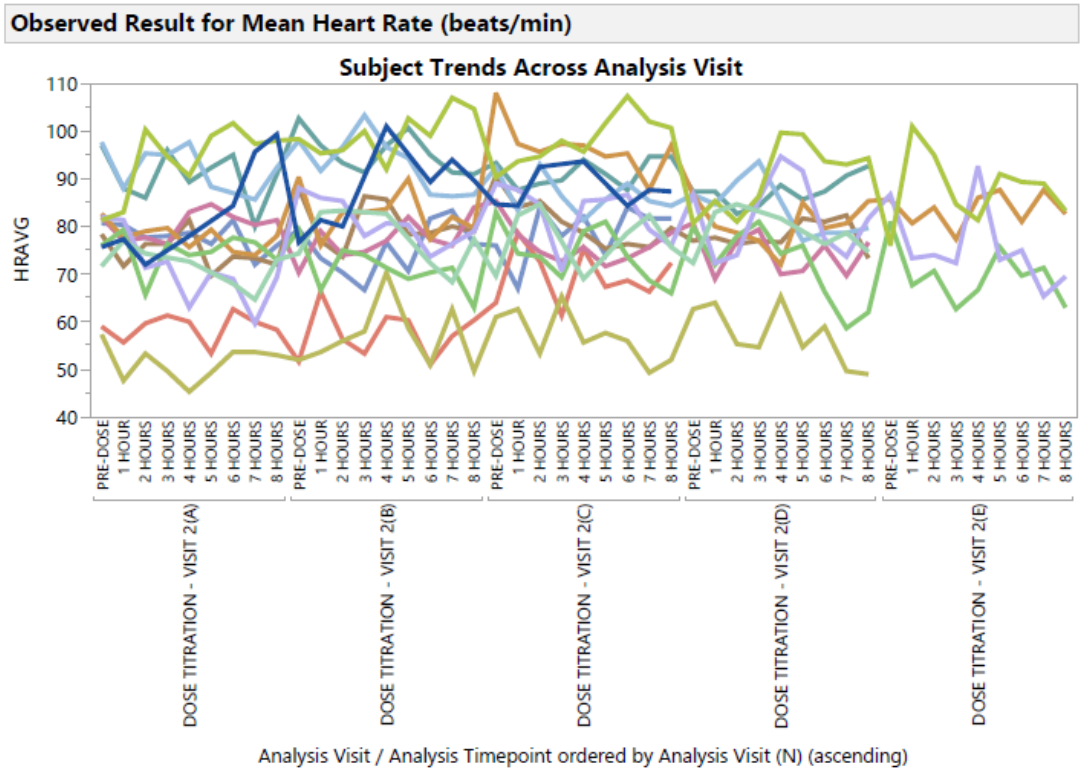


Figure 48 Subject level data Study RM-493-015




Observed Result for Mean Diastolic Blood Pressure (mmHg)
Subject Trends Across Analysis Visit
DIABPAVG
110
100
90
80
70
60
50
40
PRE-DOSE
1 HOUR
2 HOURS
3 HOURS
4 HOURS
5 HOURS
6 HOURS
7 HOURS
8 HOURS
DOSE TITRATION - VISIT 2(A)
DOSE TITRATION - VISIT 2(B)
DOSE TITRATION - VISIT 2(C)
DOSE TITRATION - VISIT 2(D)
DOSE TITRATION - VISIT 2(E)
Analysis Visit / Analysis Timepoint ordered by Analysis Visit (N) (ascending)


Observed Result for Mean Heart Rate (beats/min)
Subject Trends Across Analysis Visit
HRAVG
110
100
90
80
70
60
50
40
PRE-DOSE
1 HOUR
2 HOURS
3 HOURS
4 HOURS
5 HOURS
6 HOURS
7 HOURS
8 HOURS
DOSE TITRATION - VISIT 2(A)
DOSE TITRATION - VISIT 2(B)
DOSE TITRATION - VISIT 2(C)
DOSE TITRATION - VISIT 2(D)
DOSE TITRATION - VISIT 2(E)
Analysis Visit / Analysis Timepoint ordered by Analysis Visit (N) (ascending)

8.4.9. QT

The potential for setmelanotide to prolong the QT interval was assessed in a sub-study of patients from Studies 012, 014, and 015. Mean/median data for both QTcB and QTcF showed consistent reductions from baseline throughout the studies.

In terms of individual subject data, there are only two instances of appreciably prolonged QTc after baseline, in both cases transient ('one-off'), quite possibly due to measurement errors and of no clinical concern. The other subject (b) (6) noted as having high QTcB measurements throughout the study (>450 ms) experienced an increased QTcB to 542 ms on Day 43. This patient had a TEAE of mild hyperthermia reported the same day, and 2 days later experienced a TEAE of leukocyturia, so this increased QTcB may likely have been related to an infective process.

Part of our division's review process of this application a consult to the Interdisciplinary Review Team for Cardiac Safety Studies was placed. The consult by Dr. Christine Garnett concluded that a thorough QT study would be necessary. The IRT team found that the Applicant provided QT report based on pooled data from 57 patients across different trials, does not appear to provide
adequate quality or large exposure margin. Furthermore, (b) (4)

The conclusion of the discussions between the IRT team and DDLO resulted in an agreement to request the Applicant to submit results of a thorough TQT as a post-marketing requirement (PMR). For additional information please refer to Memorandum on file dated July 30,202 by Dr. Christine Garnett.

Proposed PMR language:
Conduct a thorough QT study to evaluate the effect of setmelanotide on the QTc interval. Design and conduct the trial in accordance with the ICH E14 guidance entitled, E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs, and its Questions and Answers.

8.4.10. Immunogenicity

To evaluate the immunogenicity of Setmelanotide the Office of Biotechnology Products was consulted primarily to assess the immunogenicity assays used for this submission. The consult's conclusion was that the anti-RM-493 ADA assay is not suitable for its intended use There was substantial intra-assay variability of the confirmatory assay and the results are uninterpretable.

The Applicant will need to address the confirmatory assay methods in order to establish reproducibility and interpretability of the resulting ADA data. A PMC to improve setmelanotide confirmatory assay reliability and reproducibility has been agreed to by the Applicant.

PMC: Improve the performance and repeatability of the setmelanotide confirmatory ADA

assay to ensure that the confirmatory ADA assay can reliably test for the presence of ADA in clinical samples.
Study Completion: May-July 2021
Final Report Submission: July-September 2021

The other assays (anti-alpha-MSH antibody assay and anti-RM-493 NAb assay are both suitable for the intended use.

8.5. Analysis of Submission-Specific Safety Issues

The events of special interest for this application were defined as AEs commonly occurring during treatment with setmelanotide (darkening of skin, sexual events, nausea, vomiting and injection site reactions) or potential mechanistic related (MC4R agonism) events such as hypertension or other events potentially impacted by centrally acting drugs such as depression and suicidal ideation, per FDA guidance.

8.5.1. Injection Site Reactions

Injection site reactions included, induration, bruising, erythema, edema, pain at the site, pruritus, bleeding, hematoma and were the most prevalent reported AEs throughout all with 26 of the 27 subjects in the safety database experiencing at least one event. Generally, these AEs were mild to moderate and self-limited. Retraining in self-administration was necessary at times, however these AEs did not lead to drug discontinuation or dropouts.

8.5.2. Darkening of Skin or Hair

All “darkening of skin or hair” events involved the skin rather than the hair and included skin hyperpigmentation, pigmentation disorder, skin discoloration, and skin striae. All such events were ongoing at last follow-up. These events were expected due to the effect of the MC1R mechanism during treatment with an MC4R agonist such as setmelanotide.
An exploratory objective was to evaluate skin color measurement in patients that participated in this specific sub-study. Skin melanin measurements at 3 body locations (forehead, zygomatic process, and right buttock) were obtained by Mexameter in this optional sub-study throughout the study. Skin darkening typically occurred 2 or 3 weeks after initiation of treatment with setmelanotide with melanin values increasing over time. TEAEs of skin hyperpigmentation were ongoing during treatment with setmelanotide. The sub study concluded that mean melanin measurements progressively increased over time in the setmelanotide treatment course.

This AE was recorded in 21 (77.8%) subjects in the safety database. AEs were generally considered mild to moderate and were ongoing at the time of data lock.
This is an expected AE of setmelanotide therapy due to co-agonism of MC1R leading to melanin stimulation. Clinically it is considered a benign AE.

8.5.3. Nausea and Vomiting

Nausea and vomiting have been reported in other MC4R agonists previously studied and were AEs of interest in the development of Setmelanotide.
Overall there were 15 (55.5%) subjects reporting at least one event of Nausea and 8 (29.6%) subjects with at least one episode of Vomiting. These AEs were mild to moderate, self-limited and did not lead to dose reduction or withdrawal.
Other GI disorders were similarly prevalent,10 (37%) subjects complaining of diarrhea and 9 (33.3%) subjects accusing abdominal pain.

8.5.4. Sexual Events

During development setmealnotide therapy resulted in sexual AEs (intermittent spontaneous penile erections and ejaculation disorder in men and disturbances in sexual arousal and genital hypersensitivity in women).
Overall, in the safety cohort there were 3 (23%) male subjects (of 13) experiencing spontaneous penile erection.

8.5.5. Hypertension

Increases in blood pressure and heart rate were considered events of interest due to previous experience with MC4R agonism compounds causing tachycardia and hypertension. There were no instances of persistent and/or clinically relevant increases in BP and HR in all clinical studies of setmelanotide.

8.5.6. Depression and Suicidal Ideation.

As with all centrally acting weight-loss drugs, depression and suicidality are AEs of interest, per FDA guidance for industry. Of the 27 subjects in the safety database, based on the original data cutoff date, there were 3 (11%) subjects that had at least one episode of depression and 3 (11%) subjects that had suicidal ideation. However, one subject ([redacted](b) (6)) had an AE of major depression that was initially counted as a separate event and did not make the initial analysis cut. Similarly, there are 4 (14%) subjects that had "depressed mood" recorded as the MeDRA preferred term.

Furthermore, a total of 13 (48%) subjects reported psychiatric disorders AEs with sleep disorder n=6 (22%) being the other prevalent AE in this category. Of the sleep disorder AEs, 4 were insomnia (15%).

For the purpose of my review, I considered the preferred terms of "depression" and "major depression" as a single AE, bring the number of subjects to 8 (30%).

Of special concern is the fact that several of these AEs were SAEs or significant AEs. For details see sections 8.4.2 and 8.4.4. Depression and suicidal ideation may be adequately addressed in labeling. Refer to Section 8.9 of this review for additional details.

8.6. Safety Analyses by Demographic Subgroups

8.6.1. Age

Age **≥6** to **≤18**

Overall the efficacy and safety in the younger patients was similar to the older patients studied. There were 9 subjects younger than 18 years of age enrolled: 6 in Study 012 and 3 in Study 015.

Based clinical pharmacology review, exposures in the 6 to <12-year-old group in general tended to be higher than those in the 12 to 17-year-old group at each setmelanotide daily dose. This was a direct result of the relationship between CL/F increasing with increasing body weight and the fixed dosing regimen. Dosing recommendations based on these results were previously covered in section 4.5.

8.6.2. Renal Disease

Setmelanotide is excreted in the urine with approximately 39% excreted unchanged. In vitro evidence demonstrates that setmelanotide is not metabolized to any degree by human kidney microsomes.

Eleven (11) subjects with mild renal impairment were included in the phase 3 studies. The popPK model suggests a trend towards 15% lower CL/F in patients with mild renal impairment, indicating a small effect of mild renal impairment on setmelanotide PK. Setmelanotide has not been studied in patients with moderate or severe renal impairment.

Per clinical pharmacology review, dose adjustment of setmelanotide is not required for mild renal impairment, however setmelanotide is not recommended in patients with moderate and severe renal impairment.

8.6.3. Hepatic Disease

In vitro evidence demonstrated that setmelanotide is not metabolized to any measurable degree by human liver microsomes (nor by human kidney microsomes or hepatocytes). No dedicated study was conducted with setmelanotide in hepatic impaired patients. With no clinical data available, setmelanotide is not recommended for use in severe hepatic impairment.

8.6.4. Pregnancy

There is no clinical data to inform regarding the effects of setmelanotide on pregnancy. Data from embryo-fetal development and pre/postnatal development studies in rats and rabbits

exposed to setmelanotide during organogenesis, at dose exposures 11 and 0.4 times respectively the exposure at the recommended human dose of 3 mg, reveal no evidence of adverse developmental effects.

A consult to the Division of Pediatric and Maternal Health was placed and the review by Dr. Jacquline Yancy concluded that (b) (4) However, since the formulation contains benzyl alcohol and the potential toxic effect of this to the fetus, the review concluded that setmelanotide is not recommended for use during pregnancy.

For additional details regarding lactation and females and males of reproductive potential see full consult by Dr. Yancy.

8.7. Specific Safety Studies/Clinical Trials

N/A

8.8. Safety in the Postmarket Setting

8.8.1. Safety Concerns Identified Through Postmarket Experience

N/A

8.8.2. Expectations on Safety in the Postmarket Setting

The safety profile of Setmelanotide in POMC/PCSK1 and LEPR was generated by the available limited data in these rare diseases and should be interpreted as such.

An integral part of the development of setmelanotide is the companion diagnostic test to accurately identify these genetic obesity patients. Setmelanotide is not indicated in subjects with obesity due to other causes other than lack of signaling through the MC4R in the context of POMC/PCSK1 or LEPR deficiency.

Furthermore, lack of efficacy should result in discontinuation of setmelanotide after a trial period of 12 weeks at therapeutic dose.

These safety measures should limit the unexpected AEs observed in postmarketing setting.

8.9. Integrated Assessment of Safety

Based on review of the available data, Setmelanotide is both safe and efficacious for treatment of obesity in patients with POMC/PCSK1 or LEPR deficiency obesity.

Overall, Setmelanotide has been well tolerated with the most common AEs being injection site reactions, skin and hair hyperpigmentation and headache and GI disorders (nausea, vomiting). Generally, these AEs have been mild and self-limited.

Additional AEs of interest observed during development of Setmelanotide, were spontaneous penile erections in males and disturbances in sexual arousal and genital

hypersensitivity in women. These AEs were mild to moderate in intensity and self-limited. There was no evidence of priapism or genital pain. Despite being generally of limited clinical importance these AEs may cause social distress to the patient and should be labeled under the warning and precautions section.

Of particular interest in the context of a centrally acting drug as Setmelanotide are the AEs of depression and suicidal ideation. Several subjects in the safety database reported these AES which were serious and led to hospitalization or other interventions. While it is true that the baseline mental health of the studied population may be poor, a direct link between setmelanotide and the occurrence of these AEs cannot be excluded at this time. As such, these AEs will be labeled under warning and precautions and providers will be instructed to monitor patients for new onset or worsening of depression and to consider discontinuing treatment if patients experience suicidal thoughts or behaviors.

Currently there are no available therapies for rare genetic disorders of obesity due to defects in the hypothalamic leptin-melanocortin pathway. POMC/PCSK1 and LEPR deficiency patients have early onset of obesity and hyperphagia. The natural history of these diseases is progressive weight gain and early development of obesity associated comorbidities.

Given the generally mild AE profile of Setmelanotide I find that the benefit of therapy in the responder population with POMC/PCSK1 or LEPR deficiency obesity far outweighs the potential for adverse reactions associated with this compound.

My assessment is based on the limited data available and should be interpreted in the context of the rare disease for which setmelanotide therapy is indicated. Extrapolation of these safety finding to the general population is not appropriate.

9 Advisory Committee Meeting and Other External Consultations

N/A

10 Labeling Recommendations

There are several important differences between the Applicant's proposed labeling and the FDA approved language for the final PI.

In Section 1 the applicant initially proposed the following language:" (b) (4) [redacted] This was adjusted to reflect the FDA analyses that only confirmed the effect on weight for this drug. Language regarding (b) (4) was removed. Additionally, (b) (4) [redacted]. Language regarding the necessity of genetic confirmation of disease

prior to therapy initiation was also added in concordance with FDA's position of the necessity of a companion diagnostic for IMCIVREE.

A Limitations of Use (LOU) section was introduced to clarify that patients with POMC, PCSK1, or LEPR variants that are classified as benign or likely benign should not be treated with IMCIVREE despite their obesity status as these subjects are unlikely to have a clinical benefit. In Section 2 additional language for the Patient Selection was introduced to align the label information to Section 1. Dosing recommendations were edited to reflect the FDA Clinical Pharmacology assessment of aligning pediatric subjects ≥12 years old to the adult dosing regimen. This is different from the initial language proposed by the Applicant (b) (4)

Important information was added in the monitoring section of the label to reflect FDA's view that a clinical evaluation of response should be performed by the prescribing physician and if the weight loss at 12 weeks is below 5% of baseline body weight to discontinue therapy.

Other clinically relevant changes in labeling were made in Section 5, Warning and precautions. The Applicant's proposed language only addressed (b) (4) erections. This section was modified to reflect the FDA conclusion that both spontaneous penile erections in males and spontaneous increase in sexual arousal in females have been documented in clinical studies IMCIVREE and that the patients should be adequately informed of these potential AEs.

For Section 5.3 the Applicant proposed the following language: (b) (4) Based on the FDA reviews this section was renamed to include Suicidal Ideation and language was added to reflect the occurrence of both depression and suicidal ideation in clinical trials with IMCIVREE.

A new section to address Skin Pigmentation and Darkening of Pre-Existing Nevi was added in the FDA final labeling. Similarly, a section to address Risk of Serious Adverse Reactions Due to Benzyl Alcohol Preservative was added to inform of the potential serious and fatal adverse reactions including "gasping syndrome" that may occur in neonates and low birth weight infants treated with benzyl alcohol-preserved drugs.

Section 6 Adverse Reactions was edited to reflect the FDA analyses and interpretation of results. There was a discrepancy between the Applicant's proposed labeling regarding the subjects analyzed for this section. The Applicant's view was that (b) (4) the FDA reviewers decided against using that cohort. As such the analyses were limited to the two pivotal trials in POMC/PCSK1 and LEPR patients.

Section 6.2, Immunogenicity, was significantly edited to reflect FDA's findings which identified ~39% of subjects screening positive for antibodies to setmelanotide and ~2% positive for antibodies to alpha-MSH. This language is different from the Applicant's proposal that (b) (4)

(b) (4)

Section 8 was redacted to reflect FDA analysis regarding potential risks associated with IMCIVREE during pregnancy. Section 8.2 was introduced to address the pediatric use. This section differs from the Applicant's submission and includes language regarding use in neonates and infants and the associated risk of exposure to IMCIVREE in this age group due to the benzyl alcohol component.

Section 8.6 was added to reflect use of IMCIVREE in renal impairment population to reflect the fact that this drug is not recommended in patients with moderate and severe renal impairment.

Section 14 was significantly modified compared to the Applicant's submission to reflect the FDA analyses and conclusions of the two pivotal trials of 52 weeks duration in POMC/PCSK1 and LEPR populations. The effects on hunger scores was edited to reflect FDA's position.
The applicant's submission proposed (b) (4) This was removed (b) (4) Instead language to reflect the numerical improvements in cardiometabolic parameters was added while highlighting that treatment effects on these parameters could not be accurately quantified statistically due to limited data available.

(b) (4)

17 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

10.2. Nonprescription Labeling

N/A

11 Risk Evaluation and Mitigation Strategies (REMS)

No Postmarketing Risk Evaluation and Mitigation Strategies (REMS) are required for approval of this application.

12 Postmarketing Requirements and Commitments

Postmarketing Requirements:

1) Complete the ongoing 26-week carcinogenicity study of setmelanotide in transgenic Tg.rasH2 mice

   Final Report Submission: January 2021

2) Conduct a thorough QT study to evaluate the effect of setmelanotide on the QTc interval. Design and conduct the trial in accordance with the ICH E14 guidance entitled, E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non- Antiarrhythmic Drugs, and its Questions and Answers (R3).

Draft Protocol Submission:	March 2021
Final Protocol Submission:	October 2021
Trial Completion:	June 2022
Final Report Submission:	December 2022

Postmarketing Commitments:

3) Improve the performance and repeatability of the setmelanotide confirmatory ADA assay to ensure that the confirmatory ADA assay can reliably test for the presence of ADA in clinical samples.

Study Completion:	May-July 2021
Final Report Submission:	July-September 2021

4) Conduct adequate analytical and clinical validation testing to establish an in-vitro diagnostic device developed to accurately and reliably detect patients with variants in the POMC, PCSK1, and LEPR genes that may benefit from setmelanotide therapy. The clinical validation should be supported by a clinical bridging study comparing the in-vitro diagnostic device and the clinical trial enrollment assays.

Final Report Submission:	November 2020

13 Appendices

13.1. All studies

Appendix Table 1 Listing of Clinical Studies:

Study	N	Population	Duration	Design	Safety
001	36	Healthy obese	2 days	DBRCT	x
002	57	Healthy obese	14 or 28 days	DBRCT	x
009	99	Healthy obese	12 weeks	DBRCT	x
026	13	Healthy obese	12 weeks	DBRCT	x
003	74	Healthy obese	90 days	DBRCT	x
008	22	Healthy obese	2 or 4 days	OL	x

006	12	Healthy obese	6 days	DBRCT	x
012	14	POMC PCSK1	52 weeks	OL with 8-week DBRCT withdrawal	√
015	13	LEPR	52 weeks	OL with 8-week DBRCT withdrawal	√
022	7	Upstream MC4R	2 years	OLE	x
011	7	POMC, LEPR	1-year increments	OLE	√
014	30	POMC, LEPR or PCSK1-heterozygous deficiency obesity POMC epigenetic deficiency obesity Bardet-Biedl Syndrome Alström Syndrome Smith-Magenis Syndrome Carboxypeptidase E Syndrome SH2B1 Haplo-insufficiency Leptin Deficiency Obesity	52 weeks	OLE	x
010	39	PWS	18 months	DBRCT	x
023	7	BBS, Alstrom Sy	69 weeks	DBRCT + OLE	x
019	1	Partial lipodystrophy	144 days	OL	x

13.2. RM-493-012

Appendix Table 2 RM-493-012 Schedule of Assessments

APPEARS THIS WAY ON ORIGINAL

Screening and Open-Label Dose Titration		
Study Period	**Screening**	**Open Label Dose Titration[1]**
Visit Number (V):	**V1**	**V2a[1]**
Start of Dose Titration Week[2] (Dose Titration Study Day ± 3 days):	**-4 to 0 (-28 to -1)**	**1 (1)**
Informed consent/Assent	X	
Inclusion/Exclusion review	X	X[3]
Medical history review	X	X[3]
Genetic Testing[4]	X	
Pregnancy test	X	X[3,5]
Physical examination[6]	X	
Height[6]	X	
Comprehensive skin exam[7]	X	
Fitzpatrick scale	X	
Open label placebo practice	X	
Dose Titration Decision[8]		X[3]
PHQ-9 & C-SSRS[9]	X	X[3]

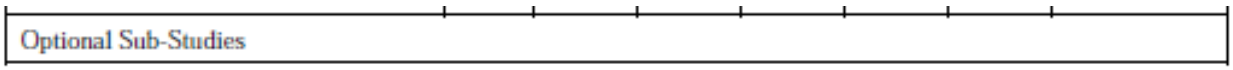
Weight/waist circumference[10]	X	X[3]
Archive sample for storage[11]	X	
Study treatment administration[12]		X
Injection site inspection[13]		X
Vital signs[14]	X	X[3,15]
ECG (12-lead)[16]	X	X[3, 16]
Safety laboratory tests[17]	X	X[3]
OGTT[18]	X	
Metabolic and Hormonal Assays[19]	X	X[20]
Biomarkers[21]	X	X[22]
HS-CRP	X	
Daily Hunger Questionnaire[23]	X	X[3]
Global Hunger Questions[24]	X	
PK blood sampling[25]		X[3,26]
Body Composition[27]	X	
Bone Age Assessment	X[28]	
Neurocognitive Assessment	X[28]	
IWQOL-Lite/PedsQL/SF-36/SF-10	X	
Anti-RM-493 antibody samples	X	X[3,29,30]
Adverse Event assessment[31]	X	X
Concomitant meds review	X	X
Telephone contact		X
Optional Sub-Studies		
24-hour PK Profile		X26
ABPM[32]	X	
Quantitative Skin Color Assessment[32], [33]	X	X3
Serial Photographs[32], [33]	X	X3
Energy Expenditure (EE)[32]	X	

10-Week Open-Label Active-Treatment / Double-Blind Placebo-Controlled Withdrawal						
Study Period		10-Week Open Label			Double Blind	
		Active Treatment[34]			Placebo-Controlled Withdrawal[34]	
	Visit Number (V):	V3	V4[35]	V5	V6	V7
	Start of Week	3	5	9	13	17
Procedure/	(Study Day):	(15)	(29)	(57)	(85)	(113)

Pregnancy test	X[5,3]	X[5,3]	X[5,3]	X[5,3]	X[5,3]
Physical examination[6]				X	
Height[6]				X	
Comprehensive skin exam[7]					
PHQ-9 & C-SSRS[9]	X[3]	X[3]	X[3]	X[3]	X[3]
Weight/waist circumference[10]	X[3]	X[3]	X[3]	X[3]	X[3]
Archive sample for storage[11]				X[3]	
Therapeutic Dose Established	X				
Study treatment administration[12]	X	X	X	X	X
Injection site inspection[13]	X	X	X	X	X
Vital signs[14]	X[3]	X[3]	X[3]	X[3]	X[3]
ECG (12-lead)[16]				X[3]	
Safety laboratory tests[17]		X[3]		X[3]	
OGTT[18]				X[3]	
Metabolic and Hormonal Assays[19]		X[3]		X[3]	
Biomarkers[21]		X[3]		X[3]	
HS-CRP				X[3]	
Daily Hunger Questionnaire[23]	X[3]	X[3]	X[3]	X[3]	X[3]
Global Hunger Questions[24]				X[3]	X[3]
PK blood sampling[25]	X[3]	X[3]	X[3]	X[3]	X[3]
Body Composition[27]				X	
IWQOL-Lite/PedsQL/SF-36/SF-1028		X[3]		X[3]	
Anti-RM-493 antibody samples		X[3, 29]		X[3, 29]	
Adverse Event assessment[31]	X	X	X	X	X
Concomitant meds review	X	X	X	X	X
Telephone contact	X	X	X	X	X
Nutritional Counseling and Monitoriing[36]		X	X		

Optional Sub-Studies					
24-hour PK blood sampling[32]					
ABPM[32]				X	
Quantitative Skin Color Assessment[32], [33]		X[37]		X	
Serial Photographs[32], [33]		X[37]		X	
Energy Expenditure[32]				X	

32-Week Open-Label Active Treatment							
Study Period	**Open Label[36]**						**Early Termination / Final Visit[37]**
	Active Treatment						
Visit Number (V):	**V8**	**V9**	**V10[35]**	**V11**	**V12[35]**	**V13**	
Start of Week:	**21**	**27**	**33**	**39**	**45**	**53**	
Procedure/ (Study Day):	**(141)**	**(183)**	**(225)**	**(267)**	**(309)**	**(365)**	
Pregnancy test	X[3, 5]	X[3, 5]	X[3, 5]	X[3, 5]	X[3, 5]	X[3, 5]	X
Physical examination[6]		X				X	X
Height[6]		X		X		X	
Comprehensive skin exam[7]				X		X	X
PHQ-9 & C-SSRS[9]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X
Weight/waist circumference[10]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X
Archive sample for storage[11]						X[3]	
Study treatment administration[12]	X	X	X	X	X	X	
Injection site inspection[13]	X	X	X	X	X	X	
Vital signs[14]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X
ECG (12-lead)[16]		X[3]				X[3]	
Safety laboratory tests[17]		X[3]		X[3]		X[3]	X
OGTT[18]						X[3]	
Metabolic and Hormonal Assays[19]		X[3]		X[3]		X[3]	X[3]
Biomarkers[21]		X[3]		X[3]		X[3]	
HS-CRP		X[3]		X[3]		X[3]	
Daily Hunger Questionnaire[23]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X
Global Hunger Questions[24]	X[3]	X[3]				X[3]	X
PK blood sampling[25]	X[3]	X[3, 26]	X[3]	X[3]	X[3]	X[3, 26]	
Body Composition[27]						X	
Bone Age Assessment						X	X
Neurocognitive Assessment						X	X
IWQOL-Lite/PedsQL/ SF-36/SF-1028		X[3]		X[3]		X[3]	
Anti-RM-493 antibody samples		X[3, 29]		X[3, 29]		X[3, 29]	X[3, 29]
Adverse Event assessment[31]	X	X	X	X	X	X	X
Concomitant meds review	X	X	X	X	X	X	X
Telephone contact	X	X	X	X	X	X	X


Optional Sub-Studies

24-Hour PK blood sampling		X[26]				X[26]	
ABPM[32]						X	
Quantitative Skin Color Assessment[32], [33]		X		X		X	
Serial Photographs[32, 33]		X		X		X	
Energy Expenditure [32]						X	

[1] The Dose Titration phase was a variable schedule lasting a minimum of 2 weeks and a maximum of 12 weeks, in which patients returned to the clinic approximately every 2 weeks in order to establish the individual patient's therapeutic dose per protocol. Given the variable number of dose titration steps in the Dose Titration Phase, each Dose Titration Visit Number (V) remained V2 with an alphabetized suffix added to each titration visit (i.e.; first dose titration at start of Week 1 = V2a, second dose titration at start of Week 3 = V2b, etc.). This allowed for Visits to be appropriately tracked. Additionally, each dose titration visit had the same pre- and post-dose assessments as outlined in the SOA (with the exception of Anti-setmelanotide antibodies and metabolic and hormonal assays).

[2] Once a patient's therapeutic dose was established per protocol, no further dose titrations occurred, and patients were to transition directly into the 10 week Open Label Active Treatment phase. Therefore, the Dose Titration phase was a minimum of 2 weeks and a maximum of 12 weeks.

[3] Prior to study drug administration.

[4] A blood sample was obtained at Screening for genotyping for mechanisms considered to be possibly related to the safety or efficacy response to the study medication (e.g., other obesity related genes).

[5] Urine pregnancy test could have been performed in order to expedite availability of results prior to dosing on Dose Titration Day 1. All other pregnancy tests were serum; dosing may have continued with results pending.

[6] A complete physical examination was conducted at screening and at the end of study. Tanner Staging for assessment of pubertal development was conducted according to the SOA for those patients who had yet to reach Tanner Stage V. Whenever possible, the same trained health care professional conducted the exam and Tanner Staging. Height was measured during the Screening Period only for those patients ≥18 years of age. Height was measured according to the SOA for those patients <18 years of age.

[7] A comprehensive skin evaluation was performed by a dermatologist. Any concerning lesions identified during the screening period were to be biopsied and results known to be benign prior to first dose of setmelanotide. If the pre-treatment biopsy results were of concern, the patient was excluded from the study.

[8] Once all the pre-dose assessments were performed, the decision to dose titrate per protocol was to be made. If the patient's therapeutic dose had been established, the patient was to transition into the 10-week Open Label Active Treatment Phase, receive their therapeutic dose, and complete the V3 post-dose assessments as defined in the SOA. If the patient's therapeutic dose has not been established per protocol, the patient was administered study drug, complete the dose titration post-dose assessments as defined in the V2 SOA, and return to the clinic in ~2 weeks for the next sequential Visit 2 (i.e.; V2b, V2c, etc.).

[9] In order to be eligible for the study, an individual patient's PHQ-9 score must have been <16 at Screening. If at any time during the study an individual patient's PHQ-9 score was ≥10, the patient was to have been referred to a Mental Health Professional (MHP). In order to be eligible for the study, at Screening, a patient was not to have a suicidal ideation of type 4 or 5, any lifetime history of a suicide attempt, or any suicidal behavior in the last month. If at any time during the study a patient had a suicidal ideation of type 4 or 5, or any suicidal behavior, the patient was to be referred to a MHP.

[10] Weight was to be measured at the clinic using the same scale after patients had emptied their bladder and while fasting. Patients were to wear light clothing or underwear, no shoes, and were weighed at approximately the same time of day. Weight measurements were to be done in triplicate; waist circumference were single measures.

[11] Extra retention samples consisted of 2 serum and 2 plasma (K2EDTA) vacutainer tubes.

[12] Study drug was administered by patients/caretakers beginning the morning of Day 1 and for the duration of dosing. Patients/caretakers were to draw up and self-administer/administer the drug once on a daily basis in the morning. On days with clinic visits, the patients/caretakers administered the drug in the clinic in the presence of the clinical staff to assure proper technique. Patients/caretakers returned all used vials to the clinic when they visited (the number recorded) and both clinic administered study drug, as well as outpatient study drug administration were recorded in a study diary.

[13] Injection site evaluations and scoring (by the clinical staff) included identification and measurement of areas of erythema, edema and induration, as well as the presence of localized pain, tenderness and itching. Additional evaluation data could have been collected at any visit where there were injection site reactions, even if not a timepoint for formal assessment.

[14] All BP and HR measurements were to be obtained in the sitting position following at least 5 minutes of rest. All measurements were taken in triplicate, approximately 2 minutes apart. When possible, BP should have been taken in the non-dominant arm throughout the study, using the same methodology (automated or manual) per protocol. Body temperature (°C) and respiration rate (breaths/minute) were obtained in the sitting position following at least 5 minutes of rest.

[15] During Day 1 and for any dose titration, vitals were collected prior to dosing and then approximately hourly post-dose for up to 8 hours.

[16] A single 12-lead electrocardiogram (ECG) was performed in the supine position following a period of at least 10 minutes of rest. On days in which dose titration occurred, measures were obtained prior to dosing and approximately 8 hours post-dose.

[17] Safety laboratories included the following: CBC with platelet count and standard indices, chemistry panel (includes sodium, potassium, chloride, CO_2, albumin, total protein, glucose, BUN, creatinine, uric acid, AST, ALT, GGT, CPK, alkaline phosphatase, total bilirubin, direct bilirubin, LDH, calcium, phosphorus), urinalysis with microscopic analysis if positive findings on dipsticks warrant further examination. Safety laboratories also included a coagulation profile (prothrombin time [PT] or international normalized ratio [INR], and partial thromboplastin time [PTT], also referred to as activated partial thromboplastin time [aPTT]. Fasting samples (8 hour minimum) were required at all timepoints where feasible. Fasting lipid panel and HbA1c were also included.

[18] Following collection of pre-meal (time 0) blood samples, patients were given a standard oral glucose tolerance test. The following blood samples were obtained during each OGTT: blood glucose and insulin at approximately 30, 60, 90 and 120 minutes after meal start.

[19] Metabolic and Hormonal Assays: assays were collected and analyzed at the time of the visit or archived for future analysis. Assays for analysis during the visit included: LH, FSH, TSH, free T4, ACTH (screening visit only), IGF-1, and IGFBP-3, serum procollagen type 1 N-propeptide, COOH-terminal telopeptide of type 1 collagen, N-terminal telopeptide of type 1 collagen, bone-specific alkaline phosphatase, osteocalcin. These samples should have been collected at the same time of day, if feasible, (e.g., between 8 AM and 10 AM) on scheduled clinic visit prior to study drug administration. Other assays (including testosterone, estradiol, GH, aldosterone, renin, cortisol and anti-inflammatory markers) were archived and measured on an as needed basis and if clinical signs or symptoms required further evaluation (e.g., renin and aldosterone were measured only if BP increases were noted).

[20] Approximately 8 hours post-dose on Day 1 only.

[21] Biomarker and high content proteomic plasma assays will be collected and archived for evaluation. Biomarker exploration testing may include neuroendocrine and endocrine markers of energy metabolism (e.g. ghrelin, leptin, insulin, orexin, oxytocin, peptide YY (PYY), GLP-1, MSH pro-insulin and BNDF) and/or anti-inflammatory markers. The discovery of protein biomarkers of POMC and PCSK1 metabolic disorders or other markers may also be explored.

[22] Approximately 8 hours post-dose.

[23] Daily hunger questionnaire scores were assessed by asking the patient to score their hunger based on a Likert-like scale, where 0 was not hungry at all and 10 was the hungriest possible. Daily hunger questionnaire scores were recorded on a daily basis, prior to the patient's morning meal.

[24] Global Hunger Questions were administered in clinic as follows: Question 1 was asked at screening, and Questions 1 and 2 were then asked as specified in the SOA once dosing has been initiated.

[25] A blood sample for PK was drawn within 5 minutes before dosing on days when dosing was performed in the clinic. These PK samples were drawn with patients/caretakers being reminded there was to be NO study drug administration at home on the day of clinic visits; the drug was administered in the clinic AFTER the PK sample was obtained. For the PK sample, the actual collection (clock) time was recorded, as well as the time of the previous day's study drug injection time as reported by the patient/caretaker.

[26] On dose titration days and defined subsequent study visits once therapeutic doses had been established as outlined in the SOA, all patients had an 8-hour PK profile obtained. A subset of patients that were logistically able to participate in a 24-hour sub-study had additional samples drawn. Blood samples were collected at 0 (within 5 minutes BEFORE dosing), 1, 2, 4, 6, 7, 8 hours (all patients) and 9, 10, 12, and 24 hours (sub-study) after dosing. The samples collected at 1 and 2 hours were collected within 5 minutes of the scheduled time; the samples at 4 to 12 hours were collected within 10 minutes of the scheduled time, and the 24-hour sample was collected within

10 minutes BEFORE the next dose of study drug. For each PK sample, the actual collection (clock) time was recorded. Patients were to have been fasting prior to the first time point collection for the 8- and 24-hour studies.

[27] Body composition may have been performed using an appropriate method available at sites (e.g. BIA, DXA, etc.) Section 6.3.3 if the protocol (Appendix 16.1.1) provided the appropriate methodology for assessing this patient population.

[28] For patients previously enrolled, the assessment was to be performed at the patient's next scheduled visit.

[29] Any patients with positive anti-drug antibodies were to be followed approximately every 3 months until titers resolved or returned to baseline.

[30] To be collected on the first two, two-week dose titration visits (V2a and V2b [or V3, if the patient's therapeutic dose had been established]).

[31] Adverse events were recorded from the time a patient provided informed consent. AEs reported after dosing on Day 1 were considered treatment-emergent AEs.

[32] Optional sub-studies for Investigative Sites that were able to carefully perform these assessments and had patients willing and able to participate. In the event a site was able to perform multiple sub-studies, care was taken to not overburden patients with multiple additional assessments/visits.

[33] For patients enrolled in France, the Quantitative Skin Color Assessments and Serial Photographs were compulsory, and not optional.

[34] Once the patient's individual therapeutic dose was established the patient entered the Open-Label Active Treatment phase for 10 additional weeks, for a combined total of 12 weeks of dosing at the therapeutic dose. During this time, the study calendar was reset, starting when the therapeutic dose was initiated (i.e. the last 2 weeks of dose titration when the therapeutic dose was established). Therefore, the Open-Label Active Treatment phase started at the beginning of Week 3 (V3). Patients losing 5 kg of weight at the end of the Open-Label Treatment phase entered the Double-Blind Placebo-Controlled Withdrawal phase lasting 8 weeks.

[35] For patients that resided a considerable distance from the clinic, these visits were optional clinic visits, and may have been performed by the patient's local physician or home health care professionals.

[36] For pediatric patients only, Nutritional Counseling and Monitoring will be performed by an appropriate dietician or nutritionist (or equivalent) to ensure that pediatric patients have adequate nutritional/dietary intake to maintain proper growth and development. Additional laboratory assessments indicative of nutritional status may be monitored, as appropriate (e.g. albumin, vitamin D, total lymphocytes and IGF1).

[37] If the visit was performed by a home health care professional, assessment may have been performed at the next schedule in clinic visit.

[38] Upon completion of the Double-Blind Placebo- Controlled Withdrawal phase, patients resumed Open-Label Active-Treatment for an additional ~32 weeks.

[39] Early Termination: For those patients who withdrew consent or were withdrawn and not willing to complete the remaining study visits, the early termination visit assessments should have been performed, when possible. Additionally, patients who withdrew and were not willing to return for the remaining clinic visits could have been contacted via phone, if amenable, to collect self-reported patient data (i.e.: weight, hunger, AEs, etc.). Final Visit: For patients who completed the study but did not wish to enroll into the future long term extension study (per protocol), patients were required to return for a Final Visit approximately 30 days after the last dose of setmelanotide, for a final follow-up safety assessment. Any ongoing AEs reported at this visit were to be monitored per protocol. For patients who enrolled into the long-term extension study, this visit was not required.

For pediatric patients only, Nutritional Counseling and Monitoring will be performed by an appropriate dietician or nutritionist (or equivalent) to ensure that pediatric patients have adequate nutritional/dietary intake to maintain proper growth and development. Additional laboratory assessments indicative of nutritional status may be monitored, as appropriate (e.g. albumin, vitamin D, total lymphocytes and IGF1).

Appendix Table 3 RM-493-012 Patient Enrollment and Disposition

Disposition	Pivotal Cohort (N=10)	Supplemental Cohort (N=4)	Total (N=14)
Study Status, n (%)			
Screened	10 (100.0)	4 (100.0)	14 (100.0)
Enrolled	10 (100.0)	4 (100.0)	14 (100.0)
Treated	10 (100.0)	4 (100.0)	14 (100.0)
Study Populations, n (%)			
Designated Use Set (DUS)1	9 (90.0)	2 (50.0)	11 (78.6)
Full Analysis Set (FAS)2	10 (100.0)	3 (75.0)	13 (92.9)
Safety Set (SAS)3	10 (100.0)	4 (100.0)	14 (100.0)
Completer's Set (CS)4	9 (90.0)	0	9 (64.3)
Per Protocol Set (PP)5	10 (100.0)	0	10 (71.4)
Study Status, n (%)			
Completed the Study	9 (90.0)	0	9 (64.3)
Completed Dose Titration Period	10 (100.0)	3 (75.0)	13 (92.9)
Completed Open Label Treatment Period #1	9 (90.0)	2 (50.0)	11 (78.6)
Completed Blinded Withdrawal Sequence	9 (90.0)	2 (50.0)	11 (78.6)
Completed Open Label Treatment Period #2	9 (90.0)	0	9 (64.3)
Withdrew from Study	1 (10.0)	1 (25.0)	2 (14.3)

Note: Percent treated and all subsequent percentages are based on the number of subjects enrolled in the study. Enrolled subjects are those with a non-missing enrollment date.
1: DUS population consists of subjects who receive any of the study drug injections, demonstrate ≥5kg weight loss or 5% of body weight if weight is < 100kg at baseline over 12-week open label treatment period, and proceed into the double-blind, placebo controlled withdrawal period.
2: FAS population consists of subjects who receive any of the study drug injections and at least one baseline assessment (includes those who do and do not demonstrate ≥ 5kg weight loss or 5% of body weight if weight is < 100kg at baseline over 12-week open label treatment period and proceed into the double blind, placebo controlled withdrawal period).
3: SAS population consists of subjects who receive any of the study drug injections and have at least one post-dose safety assessment.
4: CS population consists of all DUS subjects who demonstrate both ≥5kg weight loss or 5% of body weight if weight is < 100kg at baseline over 12-week open label treatment period and continued in the trial on active treatment to complete a full year (approximately) of treatment.
5: PP population consists of a subset of the FAS who had no major protocol violations.

Appendix Table 4 RM-493-012 Baseline laboratory data

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Appendix Table 5. Protocol Amendments

Amendment	Date	Study Sites Global/Country	Substantive Changes
Original Protocol	08 Jun 2016	Global	n/a
Amendment 1	18 Aug 2016	United Kingdom	Revised definition of females of non-childbearing potential in inclusion criterion 5, and revised inclusion criterion 6 related to male participants of childbearing potential requiring double barrier contraception
Amendment 2	01 Sep 2016	Germany	Revised highest allowable dose titration to 2.5 mg rather than 3.0 mg, and clarified dose titration during; updated inclusion 4; added exclusion 15 regarding institutionalized patients or dependents of the sponsor, Investigator or study site were ineligible for the study; and added Appendix to protocol documenting considerations specific to pediatric populations.
Amendment 3	14 Sep 2016	France	Added the same 2008 Guidance for Reducing Pain and Suffering in adolescent populations; clarified inclusion and exclusions, contraception requirements were brought into alignment with GCP/ICH Guidelines, and end of trial definition and clarification of Termination/Final Visit assessments.
Amendment 4	23 Feb 2017	Global	All country-specific revisions from previous amendments were incorporated and the following revisions added to consolidate this amendment as a global amendment: 2 Global Hunger Questions were added to the study to help assess hunger and were to be administered at clinic visits as specified within the protocol. Coagulation assessments (coagulation profile (prothrombin time [PT] or international normalized ratio [INR], and partial thromboplastin time [PTT], also referred to as activated partial thromboplastin time [aPTT])) were added to safety laboratories. The Schedule of Assessments and footnotes were updated to clarify assessments at each visit and provide information on assessments to be completed at withdrawal/early termination visits.

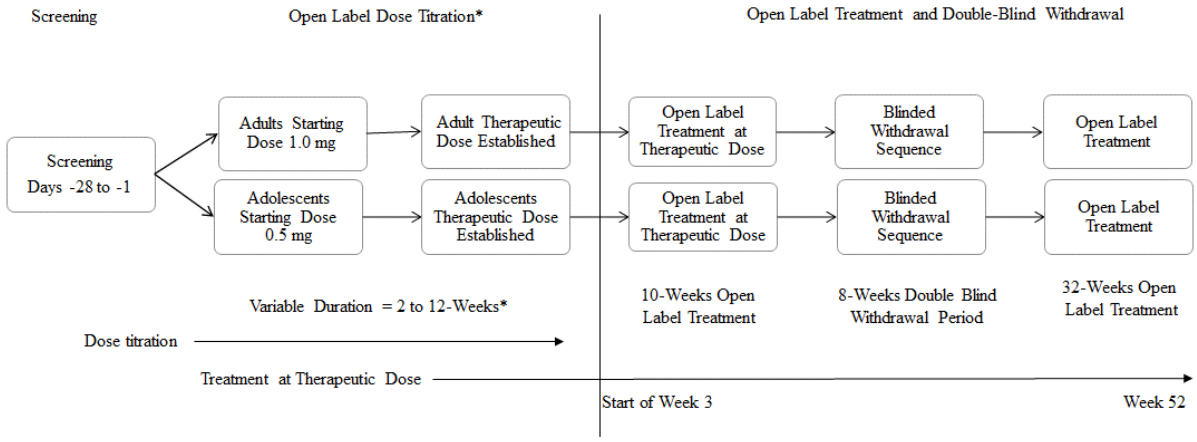
			Removed potential analytes from exploratory objectives in order to simplify procedures. Clarified which assays would be analyzed during study and those assays for analysis at a later time. Also, clarified the distinction between metabolic, hormonal assays, and biomarkers. Modified the rationale for doses selected to have the protocol encompass all competent regional authorities' requests. Modified exclusion criterion 6 to have globally acceptable language with regard to restrictive or obstructive lung disease referencing NYHA Class 3 heart failure, etc. Modified dose titration maximum allowable dose language (and duration of dose titration) to encompass all competent authorities' request. 2008 Guidance for Reducing The Pain and Suffering in the adolescent population was incorporated. This amendment incorporated country-specific revisions into a version that encompassed all competent authorities' requests to date.
Amendment 5	26 Apr 2017	France	Maximum allowable dose was revised to 2.5 mg; Quantitative Skin Assessments and Serial Photographs were made compulsory rather than optional for patients in France.
Amendment 6	22 May 2017	Global	Added inclusion of pediatric patients as young as 6 years of age; included bone age assessments; included neurocognitive assessments in patients 6 to 16 years of age; included dose titration guidelines for patients between 6 to 11 years of age; and included age appropriate hunger questions, quality of life assessments, and pediatric age range versions of C-SRS and PHQ-9.
Amendment 7	11 July 2017	Canada	Reduced number of PK sample collections for patients 6 to 11 years of age, and all blood sample volumes for all blood tests at the request of Health Canada.
Amendment 8	07 Aug 2017	Germany	Reduction in the number of PK draws for participants age 6 to 11 in order to comply with World Health Organization; Blood Sample Volumes in Child Health Research: Review of Safe Limits guidance; Inclusion of blood sample volumes for all blood tests at the request of Health Canada, and made the Quantitative Skin

			Assessments and Serial Photographs were compulsory for patients enrolled in Germany, and not optional.
Amendment 9	23 Oct 2017	USA, Canada, Germany, and United Kingdom	Reduction in the number of PK draws for participants age 6 to 11 years in order to comply with World Health Organization Blood Sample Volumes in Child Health Research: Review of Safe Limits guidance, at the request of Health Canada (implemented in Amendment 7, specific for Canada); Inclusion of blood sample volumes for all blood tests at the request of Health Canada (implemented in Amendment 7, specific for Canada), was now applicable for all sites; The Quantitative Skin Assessments and Serial Photographs were compulsory for patients enrolled in Germany and France, and no longer optional in these countries. Included at the request of Federal Institute for Drugs and Medical Devices, Germany (BfArM), (implemented in Amendment 8, specific for Germany); The top dose for participants age 6 to 11 years was revised to 2.5 mg daily, per the request of FDA (USA) and MHRA (UK); The oral glucose tolerance test (OGTT) was no longer required for patients with diabetes; Inclusion criterion 3 for pediatric and adolescent patients was revised to accurately reflect the definition of obesity in pediatric/adolescent patients. The prior criterion statement indicated a weight assessment of BMI ≥ to the 97th percentile; the criterion was revised to indicate a BMI ≥ to the 95th percentile, to correctly reflect the definition of obesity in this age group; The possibility for dose reductions for patients who met long term target weight loss goals was now to be considered, upon consultation with the sponsor; Nutritional counseling and monitoring were incorporated for all pediatric patients, in order to assure adequate nutritional intake for adequate growth and development; More frequent weight measures for pediatric patients were incorporated into the 32-week open--label period at the request of FDA; Height measurements were to be taken in triplicate, at the request of FDA; Slight modifications were

			made to the daily pediatric hunger questions, at the request of FDA.
Amendment 10	08 Nov 2017	France	This amendment included revisions from Amendment 5 (last version approved in France) through to specific revisions required by France in Amendment 10. France set youngest pediatric patients eligible to 9 years of age; starting dose for pediatric patients in France was revised to 0.25 mg; revised dose titration guidelines for patients 9 to 11 years of age; revised inclusion criterion for pediatric and adolescent patients to be related to BMI; allowance for dose reductions in patients meeting long term target weight loss goals; other revisions to approach to questionnaires and tools accommodate pediatric patients; height to be measured in triplicate; more frequent weight measures for pediatric patients; OGTT was not required for patients with diabetes.
Amendment 11	03 Apr 2018	Global (with the exception of France)	This amendment made the following revisions to amendment 4 (current version approved in the UK) Amendment 11 clarified and consolidated revisions from Amendments 9 and 10 into this document.
Amendment 12	11 Jun 2018	Canada	Clarified that all screening blood work were to be collected between Study Day -28 and -14; Included details regarding the Safety Monitoring Board that would be monitoring safety throughout the course of the study.
Amendment 13	24 Jul 2018	Global (with the exception of France)	The following revisions were changes to Amendment 11 of the protocol. Clarified that all screening blood work was to be collected between Study Day -28 and -14; Included details regarding the Safety Monitoring Board that would be monitoring safety throughout the course of the study; Included definition of Full Analysis set in the Statistical Procedures.

13.3. RM-493-015

Appendix Table 6 Study Schema



*The last two weeks of the Open Label Dose Titration Phase in which the therapeutic dose for an individual patient is established will be considered the first two weeks of Open Label Treatment. Subsequently patients will then receive an additional 10 weeks of active treatment in the Open Label Treatment for a total combined duration of 12 weeks, before transitioning into the Double Blind Withdrawal Phase.

Appendix Table 7 Schedule of Assessments

Screening and Open-Label Dose Titration		
Study Period	**Screening**	**Open Label Dose Titration[1]**
Visit Number (V):	**V1**	**V2a[1]**
Start of Dose Titration Week[2] (Dose Titration Study Day ± 3 days):	**-4 to 0 (-28 to -1)**	**1 (1)**
Informed consent/Assent	X	
Inclusion/Exclusion review	X	X[3]
Medical history review	X	X[3]
Genetic Testing[4]	X	
Pregnancy test	X	X[3,5]
Physical examination[6]	X	
Height[6]	X	
Comprehensive skin exam[7]	X	
Fitzpatrick scale	X	
Open label placebo practice	X	
Dose Titration Decision[8]		X[3]
PHQ-9 & C-SSRS[9]	X	X[3]
Weight/waist circumference[10]	X	X[3]
Archive sample for storage[11]	X	

Screening and Open-Label Dose Titration		
Study Period	**Screening**	**Open Label Dose Titration[1]**
Visit Number (V):	**V1**	**V2a[1]**
Start of Dose Titration Week[2] (Dose Titration Study Day ± 3 days):	**-4 to 0 (-28 to -1)**	**1 (1)**
Study treatment administration[3]		X
Injection site inspection[4]		X
Vital signs[5]	X	X[3,6]
ECG (12-lead)[7]	X	X[3,7]
Safety laboratory tests[8]	X	X[3]
OGTT[9]	X	
Metabolic and Hormonal Assays[10]	X	X[11]
Biomarkers[12]	X	X[13]
HS-CRP	X	
Daily Hunger Questionnaire[14]	X	X[3]
Global Hunger Questions[15]	X	
PK blood sampling[16]		X[3,17]
Body Composition[18]	X	
Bone Age Assessment	X[19]	
Neurocognitive Assessment	X[19]	
IWQOL-Lite/PedsQL/SF-36/SF-10	X	
Anti-RM-493 antibody samples	X	X[3,20,21]
Adverse Event assessment[22]	X	X
Concomitant meds review	X	X
Telephone contact		X
Optional Sub-Studies		
24-hour PK Profile		X17
ABPM[23]	X	
Quantitative Skin Color Assessment[23], [24]	X	X3
Serial Photographs[23], [24]	X	X3
Energy Expenditure[23]	X	

10-Week Open-Label Active-Treatment / Double-Blind Placebo-Controlled Withdrawal					
Study Period	10-Week Open Label			Double Blind	
	Active Treatment[25]			Placebo-Controlled Withdrawal[25]	
Visit Number (V):	V3	V4[26]	V5	V6	V7
Start of Week	3	5	9	13	17
Procedure/ (Study Day):	(15)	(29)	(57)	(85)	(113)
Pregnancy test	X[5,3]	X[5,3]	X[5,3]	X[5,3]	X[5,3]
Physical examination[6]				X	
Height[6]				X	
Comprehensive skin exam[7]					
PHQ-9 & C-SSRS[9]	X[3]	X[3]	X[3]	X[3]	X[3]
Weight/waist circumference[10]	X[3]	X[3]	X[3]	X[3]	X[3]
Archive sample for storage[11]				X[3]	
Therapeutic Dose Established	X				
Study treatment administration[3]	X	X	X	X	X
Injection site inspection[4]	X	X	X	X	X
Vital signs[5]	X[3]	X[3]	X[3]	X[3]	X[3]
ECG (12-lead)[7]				X[3]	
Safety laboratory tests[8]		X[3]		X[3]	
OGTT[9]				X[3]	
Metabolic and Hormonal Assays[10]		X[3]		X[3]	
Biomarkers[12]		X[3]		X[3]	
HS-CRP				X[3]	
Daily Hunger Questionnaire[14]	X[3]	X[3]	X[3]	X[3]	X[3]
Global Hunger Questions[15]				X[3]	X[3]
PK blood sampling[16]	X[3]	X[3]	X[3]	X[3]	X[3]
Body Composition[18]				X	
IWQOL-Lite/PedsQL/SF-36/SF-1019		X[3]		X[3]	
Anti-RM-493 antibody samples		X[3,20]		X[3,20]	
Adverse Event assessment[22]	X	X	X	X	X
Concomitant meds review	X	X	X	X	X
Telephone contact	X	X	X	X	X

10-Week Open-Label Active-Treatment / Double-Blind Placebo-Controlled Withdrawal					
	10-Week Open Label			Double Blind	
Study Period	Active Treatment[27]			Placebo-Controlled Withdrawal[25]	
Visit Number (V):	V3	V4[28]	V5	V6	V7
Start of Week	3	5	9	13	17
Procedure/ (Study Day):	(15)	(29)	(57)	(85)	(113)
Optional Sub-Studies					
24-hour PK blood sampling[23]					
ABPM[23]				X	
Quantitative Skin Color Assessment[23], [24]		X[29]		X	
Serial Photographs[23], [24]		X[29]		X	
Energy Expenditure[23]				X	

32-Week Open-Label Active Treatment							
Study Period	Open Label[30]						Early Termination / Final Visit[31]
	Active Treatment						
Visit Number (V): / Start of Week: / Procedure/ Day): (Study)	V8 21 (141)	V9 27 (183)	V10[26] 33 (225)	V11 39 (267)	V12[26] 45 (309)	V13 53 (365)	
Pregnancy test	X[3, 5]	X[3, 5]	X[3, 5]	X[3, 5]	X[3, 5]	X[3, 5]	X
Physical examination[6]		X				X	X
Height[6]		X		X		X	
Comprehensive skin exam[7]				X		X	X
PHQ-9 & C-SSRS[9]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X
Weight/waist circumference[10]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X
Archive sample for storage[11]						X[3]	
Study treatment administration[3]	X	X	X	X	X	X	
Injection site inspection[4]	X	X	X	X	X	X	
Vital signs[5]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X
ECG (12-lead)[7]		X[3]				X[3]	
Safety laboratory tests[8]		X[3]		X[3]		X[3]	X
OGTT[9]						X[3]	
Metabolic and Hormonal Assays[10]		X[3]		X[3]		X[3]	X[3]
Biomarkers[12]		X[3]		X[3]		X[3]	
HS-CRP		X[3]		X[3]		X[3]	
Daily Hunger Questionnaire[14]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X
Global Hunger Questions[15]	X[3]	X[3]				X[3]	X
PK blood sampling[16]	X[3]	X[3, 17]	X[3]	X[3]	X[3]	X[3, 17]	
Body Composition[18]						X	
Bone Age Assessment						X	X
Neurocognitive Assessment						X	X
IWQOL-Lite/PedsQL/ SF-36/SF-1019		X[3]		X[3]		X[3]	
Anti-RM-493 antibody samples		X[3, 20]		X[3, 20]		X[3, 20]	X[3, 20]
Adverse Event assessment[22]	X	X	X	X	X	X	X

32-Week Open-Label Active Treatment							
Study Period	Open Label[32]						Early Termination / Final Visit[33]
	Active Treatment						
Visit Number (V):	V8	V9	V10[26]	V11	V12[26]	V13	
Start of Week:	21	27	33	39	45	53	
Procedure/ (Study Day):	(141)	(183)	(225)	(267)	(309)	(365)	
Concomitant meds review	X	X	X	X	X	X	X
Telephone contact	X	X	X	X	X	X	X
Optional Sub-Studies							
24-Hour PK blood sampling		X[17]				X[17]	
ABPM[23]						X	
Quantitative Skin Color Assessment[23], [24]		X		X		X	
Serial Photographs[23, 24]		X		X		X	
Energy Expenditure [23]						X	

Additional Secondary, Tertiary and Exploratory Endpoints
The following additional secondary, tertiary, and exploratory endpoints were included in the original study protocol.

- The safety and tolerability of treatment with setmelanotide
- Hunger was assessed daily throughout the study; patients ≥12 years of age self-report their hunger by responding to three questions and patients 6 to 11 years of age self-report their hunger each morning just prior to dosing by responding to one question
- Two global hunger questions were administered to assess patients' perceptions of their current status and change from baseline at key time points
- Glucose parameters
- Waist circumference.
- Lipids
- For patients ≥18 years of age, health related quality of life (HRQOL) was assessed using the validated condition specific self-report instrument the Impact of Weight on Quality of Life-Lite (IWQOL-Lite) and the self-report instrument SF-36 was used to measure functional health and well-being.
- For patients <18 years of age, general HRQOL was assessed with the validated Pediatric Quality of Life Inventory (PedsQL) and SF-10 for patient self-report and caregiver-reported assessment.
- Changes in pubertal development
- Changes in growth and development
- Limited number of patients were expected to participate in various sub-studies (ABPM, skin color quantification, energy expenditure, and 24-hour PK profile); therefore, it was anticipated that no

definitive conclusions would be determined regarding the effects of setmelanotide on these parameters. However, trends over time were explored.

- Metabolic and hormonal assays were collected and analyzed to assess neuroendocrine aspects and responses to therapy.
- Changes in depression/suicidality as assessed by the C- SSRS and PHQ-9 were monitored.
- Specific guidelines for dermatological events, liver function abnormalities, and penile erections were specified in the protocol.
- The PK of setmelanotide in plasma was assessed in patients (except pediatric patients 6 to 11 years of age) by trough (pre-dose) concentrations measured prior to each dose administered in the clinic.
- Biomarkers and high content proteomic plasma assays predictive of a setmelanotide response, or as a measure of the setmelanotide target engagement were to be potentially evaluated.

Appendix Table 8 Protocol Amendments

Amendment	Date	Study Sites Global/Country	Substantive Changes
Original Protocol	30 May 2017	Global	n/a
Amendment 1	11 September 2017	France	This amendment incorporated revisions which addressed feedback received following the review by the French Agency for the Safety of Medicinal and Health Products (ANSM). These changes were considered for a future global amendment across all sites, but Amendment 1 only applied to France. The major revisions in this amendment were the following. • Limited the maximum possible dose to 2.5 mg (from 3.0 mg), which impacted the potential number of dose titration steps (5 versus 6) resulting in an updated duration (10 weeks versus 12 weeks) in the dose titration phase of the study. • Made “quantitative skin color assessment” and “serial photographs” compulsory assessments for all patients in France. • The text was clarified to indicate that a dual method of contraception was utilized in the study.
Amendment 2	27 September 2017	Germany	Protocol amendment 2 incorporated revisions which addressed feedback received following the review by the Federal Institute for Drugs and Medical Devices in Germany (BfArM) and the German Ethics Committee. Some of these changes were considered for a future global amendment across all study centers, but Amendment 2 only applied to Germany. The

			following revisions were the major changes made compared to the original protocol. From BfArM Review: • Limited the maximum possible dose to 2.5 mg (from 3.0 mg), which impacted the potential number of dose titration steps (5 versus 6) resulting in an updated duration (10 weeks versus 12 weeks) in the dose titration phase of the study. • Included updated clinical data on LEPR patients 1, 2 and 3 from study RM-493-011 in the clinical background section of protocol Section 1.2.2 • Clarified reporting requirements as per ICH E6 R2 and the EU Clinical Trials Directive (2001/20/EC) From German Ethics Committee Review: • Provided examples of significant types of hypersensitivity reactions in exclusion criterion #13.
Amendment 3	10 April 2018	Global)	Protocol 3 was a global protocol amendment applicable to all study sites; it was based upon Amendment 2 which was only submitted to Germany. Substantive revisions made in Amendment 3 were as follows: • Inclusion Criterion #2 was revised to include patients ≥6 year of age and provided dose titration instructions and other applicable revisions to accommodate this younger patient population. • Revised the primary endpoint to a proportion of patients who met ≥10% weight loss rather than mean percent change from baseline. • Confirmed that more than10 patients may have been enrolled if additional eligible patients were identified. • Clarified that OGTT was not to be performed for patients with a diagnosis of Type 1 or Type 2 diabetes. • Clarified that the schedule for obtaining samples for anti-drug antibodies was to be at Day 15 and Day 29 after initiation of dosing rather than on Day 15 and Day 29 after establishing the therapeutic dose. • Addition of QOL questionnaires SF-10, PedsQL, and C-SSRS (age-specific for patients ≥6 years of age. • Added bone X-rays. • Added WIXD-V neurocognitive assessment.

			• Added an appendix that summarized blood volumes required for study assessments. • Added nutritional counseling for pediatric patients. • Clarified that for patients <100 kg at baseline, a 5% change in weight was required to continue with study treatment rather than a 5 kg change in weight for >100 kg at baseline.
Amendment 4	31 July 2018	Global	Protocol Amendment 4 was a global protocol amendment applicable to all study sites; it was based upon Amendment 3. Substantive revisions made in Amendment 4 were as follows. • Clarified that all Screening blood analyses were to be collected between Day -28 and Day -14. • Provided details regarding the Safety Monitoring Board used to monitor safety throughout the study to align with the current SAP at the request of the US Food and Drug Administration (FDA). • Clarified bone assessment schedule by adding a footnote that confirmed that bone age assessment was only required at the early termination visit and not at the final visit, as requested by the German Ethics Committee.
Addendum	26 November 2018	Global	The purpose of the protocol addendum was to allow patients that experienced an adverse event or abnormal laboratory value an opportunity to be re-challenged with vehicle control (placebo) or lower doses of setmelanotide to further assess relatedness to study drug. If the Investigator wanted to further assess relatedness to study drug, the patient could have been re-challenged after approval by the Sponsor. Prior to re-challenging any patient, the Sponsor and Investigator were to define a re-challenge plan with certain parameters, specific to a particular patient. The addendum provided guidance and instructions to be followed when re-challenging a patient and assessing the data obtained during the re-challenge.

Appendix Table 9 Patient Enrollment and Disposition

Disposition	Pivotal Cohort (N=11)	Supplemental Cohort (N=2)	Total (N=13)
Study Status, n (%)			
Screened	11 (100.0)	2 (100.0)	13 (100.0)
Enrolled	11 (100.0)	2 (100.0)	13 (100.0)
Treated	11 (100.0)	2 (100.0)	13 (100.0)
Study Populations, n (%)			
Designated Use Set (DUS)[1]	7 (63.6)	1 (50.0)	8 (61.5)
Full Analysis Set (FAS)[2]	11 (100.0)	2 (100.0)	13 (100.0)
Safety Set (SAS)[3]	11 (100.0)	2 (100.0)	13 (100.0)
Completer's Set (CS)[4]	6 (54.5)	0	6 (46.2)
Per Protocol Set (PP)[5]	8 (72.7)	0	8 (61.5)
Study Status, n (%)			
Completed the Study	9 (81.8)	0	9 (69.2)
Completed Dose Titration Period	11 (100.0)	2 (100.0)	13 (100.0)
Completed Open Label Treatment Period #1	8 (72.7)	1 (50.0)	9 (69.2)
Completed Double-blind, Placebo-controlled Withdrawal Sequence	8 (72.7)	1 (50.0)	9 (69.2)
Completed Open Label Treatment Period #2	9 (81.8)	0	9 (69.2)
Withdrew from Study	2 (18.2)	0	2 (15.4)
Primary Reason for Early Withdrawal, n (%)			
Adverse Event	1 (9.1)	0	1 (7.7)
Death	1 (9.1)	0	1 (7.7)

APPEARS THIS WAY ON ORIGINAL

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

OVIDIU A GALESCU
11/24/2020 10:41:39 AM

JOHN M SHARRETTS
11/24/2020 10:49:57 AM
I concur with the findings of the review, including the conclusions regarding approval and labeling.